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SUPPLEMENTUM 18

THE HUMORAL SYSTEM OF THE LABYRINTH

A correlation study in the cat and Dalmatian dog between ion chemistry of labyrinthine fluids and microphonic function of the cochlea

A critical discussion of the literature and a presentation in table-form of the multiple aspects of labyrinthine fluids concerning cochleo-vestibular physiology

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A CRITICAL DISCUSSION OF THE LITERATURE AND A PRESENTATION IN TABLE FORM OF THE MULTIPLE ASPECTS OF LABYRINTHINE FLUIDS CONCERNING COCHLEO VESTIBULAR PHYSIOLOGY

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o my peerless wife Wanda with love and respect

o my father Prof Pietro Maggio and my mother Prof Maria Maggio Galgano with gratitude for their encouragement and assistance

"Quoties enim auris recentissima et integra, nec dimoto stapede ad observandum affumitur, dum levitur stapes de fenestra ovali subducitur, totum vestibulum aqua plenissimum observatur.

'Quam pessime igitur ibi Natura confuluisset si non humore, sed aere plenum, ut vulgaris opinio fert, fecisset labyrinthum.

DOMENICO COTUGNO

From "De Aquaeductibus Auris Humanae Internae Anatomica Dissertatio" Neapoli et Bononiae. Ex Typographia Sancti Thomae Aquinatis 1775

Translation from Latin

"In fact any time a fresh and undamaged ear preparation is observed, the stapes having not been removed but only partially lifted from the oval window the entire vestibule appears full of water."

How inefficient Nature would have provided herself should air, as generally accepted, rather than fluid, fill the labyrinth."

Foreword

It is surprising that the attention of scientists and clinicians for labyrinthine fluids has been so little in recognizing them as an humoral system similar to other specialized fluid systems of the body that even in the most complete and up-to-date treatises of physiology and otolaryngology they appear underemphasized and often neglected. On the other hand from Cotugno's discovery in 1761 that the inner ear cavities are filled with fluid rather than air a great number of investigations has been carried out to establish the nature, origin and significance of labyrinthine fluids in cochleo-vestibular physiology This type of investigation however produced more hypotheses and theories than proved facts primarily because the variables of cochlear and vestibular functions — among which the physical chemical and electrophysiologic properties of endolymph and perilymph seem to play a crucial role — have not been studied in correlation with each other From what has been said one could also understand why the literature is in general confusing and often contradictory

In presenting this monograph « The Humoral System of the Labyrinth » it is our aim to put the right emphasis on the fluids of the ear and their role in hearing and equilibrium on the basis of our own studies and a detailed critical review of the most significant literature The first and fundamental step of an extensive research project on labyrinthine fluids by which we interested a large number of people at the University of Illinois in Chicago during the last three years has been the correlation study between ion chemistry of labyrintrine fluids and bioelectric phenomena of the cochlea. The results obtained support our belief that the inner ear fluids are the essential factor in the conversion of the mechanical energy (of the specific stimuli. sounds and movements of the body in the space) into electric energy by the end-organs of the labyrinth. Dynamic relationships have been demonstrated between sodium and potassium concentration in perilymph and microphonic potential of the cochlea in cats and Dalmatian dogs It seems possible therefore, to predict the hearing capacity of the cochlea from the ion chemistry of perilymph an vice versa. By carrying out this correlation in man at the time of surgery new avenues may be open for the diagnosis and theatment of labyrinthine disorders. We believe that by investigating the mysteries of the ear in the above way a day may come in which "labyrinth" would not be the accurate term at least in a physiologic sense for what is still one of the most intricate entities of the body On that day the labyrinth of the ear will be better known and no longer considered a maze without safe exists such as that which Dedalus built in Crete to imprison the Minotaur

Elio Maggio

New York, 1966

Acknowledgments

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The conduction of the electrophysiologic experiments the method of analysis of cochlear microphonic potential and the statistical evaluation of the data have been done in cooperation with A J Derbyshire Ph.D

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CHAPTER I

Historical development of the studies on the humoral system of the labyrinth and general considerations of the fluids and electric biopotentials of the inner ear

The fluids which fill the cavities of the inner ear i.e endolymph in the membranous labyrinth and perilymph in the space surrounding it were discovered by the Italian anatomist Domenico Cotugno (76) in 1761 and called labyrinthine fluids only in 1949 by the German otologist Franz Kobrak (192) They form a sort of humoral system which in some respects is similar to that formed in the central nervous system by cerebrospinal fluid and in the eye by aqueous humor Figure 1 is a diagrammatic representation of the anatomophysiologic relationships between labyrinthine fluids blood and cerebrospinal fluid Direction and magnitude of the arrows indicating those relationships must be experimentally demonstrated It is conceivable, however that a complex biologic equilibrium exists between the humoral system of the labyrinth and the two other fluid media mentioned before as a fundamental aspect of the neurosensory function of the inner ear

According to recent electronmicroscopic studies (106 109) a third fluid seems to exist in the labyrinth within the spaces of the organ of Corti and called, therefore cortilymph by Engström (106) Since this fluid is still under investigation from both anatomical and physiologic viewpoints it is not included within labyrinthine fluids in this presentation. Any information concerning cortilymph however will be reported and discussed in this chapter (see page 18)

Cotugno (76) not only first demonstrated that fluid not air was contained in the labyrinth but also first believed that the fluid found in the cochlea was related to the function of hearing A few years after his discovery the German anatomist J Meckel Sr (quoted by von Békésy loc. cit. 35), confirmed the presence of fluid in the inner ear During the opening of a cat temporal bone under water in fact he found that no air bubbles came up from labyrinthine cavities. The structure of the cochlea as being applicable to hearing was first recognized by the French anatomist J G Duverney (100), in 1683 The vibrating mechanism whose existence in the cochlea was ascribed to the Frenchman Perrault (282) in 1680 was thought by Duverney to be located in the bony spiral lamina and to respond in its various sections to different tones according to the resonance principle. Be

cause of the broader extension at the base and the gradual narrowing up to the apex, the perception of low tones and high tones was located respectively at the base and apex of the spiral lamina. Concerning the function of equilibrium, credit must be given to the French physiologist J.P.M. Flourens (129), who in 1824 first demonstrated that the membranous labyrinth is also the site of the sensory organ of equilibrium. His experiments on the effects on head and body movements of sectioning one or more semicircular canals in pigeons are classic in vestibular physiology.

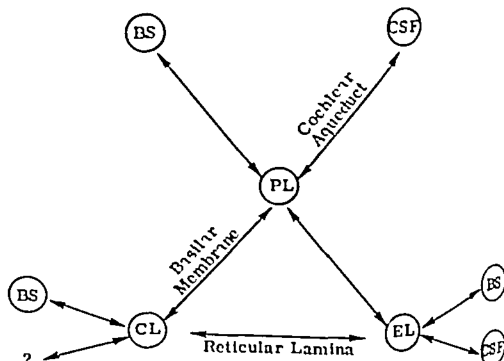


Fig. Diagrammatic representation of the anatomophysiologic relationships between labyrinthine fluids, blood and cerebrospinal fluid. PL perilymph. EL endolymph. CL cortilymph. BS blood. CSF cerebrospinal fluid.

Perilymph fills the space surrounding the cochlea and vestibule, which is called therefore perilymphatic space. This communicates with the perineural and perivascular spaces in the internal auditory meatus and with the subarachnoid space through the cochlear aqueduct whose opening in scala tympani is close to the round window. The endothelial mesh of the arachnoid extends from the posterior cranial fossa to the round window. This anatomical way of communication between intracranial environment and that of labyrinthine cavities is much longer and more narrow in man and monkey than in other vertebrates. In addition, the passage of fluid in the cochlear aqueduct is assumed to be similar to that in a tube filled with cotton. A true septation originating from the arachnoid web was

first described by Waltner (414) in 1948 as a "barrier membrane between peri lymph and cerebrospinal fluid The physiologic significance of these structural charac teristics of the inner ear was traditionally considered to be the prevention of too great and especially too sudden variations of labyrinthine pressure in relation to changes in intracranial pressure which occur in man during passage from prone to erect posture, and vice versa Recent studies (344) however indicate that the cochlear acqueduct is apparently not necessary for the maintenance of perilymph volume. They also indicate that cochlear function may be preserved in the pre sence of free communication between endolymph and perilymph

The perilymphatic space, in the cochlea consists of two parts or scalae, divided by a third scala or scala media which is the membranaus cochlear duct containing the organ of Corti and the other labyrinthine fluid, the endolymph The upper scala, or scala vestibuli is divided from the middle ear cavity by the foot plate of the stapes in the niche of the oval window The lower scala or scala tympani is divided from the middle ear cavity by the round window membrane. Both perilymphatic scalae communicate with one another at the apex of the cochlea through a semilunar opening between the free curved edge of the modiolar lamina and the hamulus of the scala spiralis ossea the so-called helicotrema.

The membranous labyrinth contains endolymph and is surrounded by the perilymphatic space full of perilymph. Endolymph is more similar to a gelatinous mass than to a true fluid because of its viscosity especially in some animal species such as the fishes of the selachian family (elasmobranchs) (see Table II). In the cochlea, it is contained in the membranous cochlear duct and in the ductus reuniens of Hensen which connects the saccule with the blind end (vestibular cecum) of the cochlear duct In the vestibule endolymph is contained in the sac cule utricle, utriculo-saccular duct the three semicircular canals the endolymphatic duct and the endolymphatic sac This sac lies under the brain in the posterior cranial fossa within two split layers of the dura mater close to the transverse venous sinus The endolymphatic duct is contained in the bony vestibular aque duct, i.e a vestibular structure which is analogous to the cochlear aqueduct in the cochlea. The endolymphatic duct is believed to offer some protection to the laby rinth against the too great and too sudden variations of intracranial pressure

Another structure which may display a protective function for the labyrinth is the utriculo-endolymphatic valve, a valve shaped reflection of the utriculo-sac cular duct which was first described by the American anatomist Bast (30), in 1928 When closed it would divide an anterior portion of the membranous labyrinth formed by the cochlea and saccule from a posterior part formed by the utricle semicircular canals and endolymphatic duct and sac. It is conceivable that in case of increase in pressure within the anterior membranous labyrinth the utriculo-endolymphatic valve would close and protect the posterior labyrinth from the effects of hypertension. The membranous labyrinth was believed to be an open system before 1861 when the Swiss histologist, von Kölliker (193) recognized the existence of scala media or canalis coclearis This was first described by the German anatomist, Ernst Reissner (324) after the discovery of the membrane

separating endolymph in scala media from perilymph in scala vestibuli. At that time the perilymphatic space was interpreted as a simple diverticulum of the cochlear aqueduct and therefore to have free communication with the subarachnoid cistern. The boundary limit of the scala media from the scala tympani is formed by the basilar membrane only from the anatomical viewpoint from the electrochemical standpoint in fact, the reticular lamina of the organ of Corti seems to be the deviding structure. This will be discussed in detail on page 39

Concerning cortilymph i e. the hypothesized third fluid of the inner ear both anatomical and physiologic informations are very few The authors who first described cortilymph within the spaces of the organ of Corti by electron microscopy (109) consider it a fluid completely isolated from endolymph by the reticular lamina of the organ of Corti No communication in fact has been observed between the scala tympani and the scala media either during embryologic development or adult life (106) According to more recent investigations (345) which do not seem to support this hypothesis perilymph would pass from scala tympani into the spaces of the organ of Corti. By a histochemical method for the enzyme acetylcholinesterase (precipitation of copper in the region of the auditory nerve terminals at the level of the hair cells) in fact a dense even fine deposit has been demonstrated along the lower shelf of the bony spiral lamina toward the scala tympani (345) The existence in this region of a system of tiny canals directed toward the habenula perforata (through which the auditory nerve terminals meet the hair cells) has been hypothesized (345).

The possibility that perilymph and cortilymph although not identical are at least very similar to each other is also supported by the fact that the protein concentration and the ratio sodium/potassium ions of the fluid filling the spaces of the organ of Corti are closer to those of the perilymph of the scala tympani than to those of the endolymph of the scala media (313) Assuming that cortilymph does not exist as a third cochlear fluid, the perilymph contained in the spaces of the organ of Corti may be a modified perilymph, i.e. it may be perilymph of the scala tympani modified by the metabolic activity of the hair cells and supporting cells of the organ of Corti. Conversely by assuming that cortilymph really exists as a fluid different from perilymph and endolymph it would be interesting to investigate its embryologic origin and the possibilities that the system of tiny channels between the scala tympani and the organ of Corti via the osseous spiral lamina may serve as a drainage of cortilymph depending upon the levels of the hydrostatic and osmotic pressures in the cochlea. In the original interpretation of Engström and Wersäll (109) the problem of the origin and drainage of cortilymph was theoretically approached by considering some morphologic characteristics of Hensen's and Deiter's cells Finger-like protrusions (microvilli) directed toward endolymph have been seen on these cells. Since these structures are similar to those which are usually observed on the surfaces of other reabsorptive structures (the cells of the small intestine the epithelium of renal tubules and that of the olfactory region for example) the hypothesis of an absorptive function of Hensen's and Deiter's cells has been forwarded (109) However no alkaline phosphatase activity

has been found (297) in the filiform processes of Hensen's cells as would be expected assuming their significance as reabsorptive structures. The rationale for this consideration is that alkaline phosphatase is very high in structures devoted to absorption processes (297).

*

An impressive anatomophysiologic difference between the *anterior and posterior* labyrinth is represented by the mode by which the nourishment of labyrinthine neuroreceptors is accomplished. In general the blood supply of cochlear and vestibular neuroepithelium is moderately rich, like that of any other neurosensory structure. In the cochlea however no vessels have been seen to reach the hair cells. The role which may be played in the nutrition of the organ of Corti by the series of arcades running beneath the tunnel of Corti and which appear in histologic sections as a spiral vessel has been considered only recently as a problem worth of attention. According to Lawrence (209 b c), "The arcades of vessels beneath the basilar membrane are the essential source of nutrients of these sensory cells." instead of the vessels of the stria vascularis af first believed by Corti in 1851 and since by most otologists. The occlusion of the blood vessels passing from the modiolus to the stria vascularis resulted in the degeneration of the stria but did not damage the organ of Corti. On the other hand, the occlusion of the blood vessels passing beneath the basilar membrane resulted in the degeneration of the hair cells of the organ of Corti but did not alter the stria vascularis and the spiral prominence. The experiments were made possible by introduction of a probe having a tip of 75 micra in diameter through a hole honed in the scala vestibuli, and by studying temporal bone sections of the guinea pigs sacrificed 4-6 weeks after vascular occlusion in the cochlea. As a conclusion of these studies Lawrence also states that "These minute looping vessels" (under the basilar membrane) so small that they let only one blood cell through at a time must be kept open if the organ of Corti is to function. ( ) *Even by assuming that these vessels and not those of the stria vascularis are the essential nutrient channels for cochlear neuroepithelium the blood supply cannot be considered as direct like that of vestibular neurosensory*

( ) The emphasis put by Lawrence on the vascular arcades running beneath the basilar membrane as the essential source of nutrition to the organ of Corti led him to consider another problem which deserves attention in clinical otology the possibility of controlling hearing disorders by drugs usually employed in the management of disfunctions of the autonomic nervous system. As matter of fact, though no nerve fibres have been demonstrated on the vessels under the basilar membrane, as well as on those of the stria vascularis, they exist in the modiolus and, according to Lawrence, their connection with the looping capillaries beneath the basilar membrane could be demonstrated by further research. This could be valuable confirmation of concept expressed by us several years ago, i.e., that certain hearing disorders, such those of otosclerosis and Menière disease for example, could be related to the impairement of the local neuro-humoral control of microhemocirculation, as an expression in the cochlea and-or in the

end-organs because of the presence of fluid between the microvascular loops running beneath the basilar membrane and the cells of the organ of Corti In the ampullary cristae of the semicircular canals and in the maculae of utricle and saccule, conversely the subepithelial capillary networks are in direct contact with the neurosensory epithelium

Concerning the mechanism by which labyrinthine neuroreceptors are stimulated and the mechanical energy of the specific stimuli is converted by them into electric energy no significant differences seem to exist between cochlea and vestibule As a matter of fact, the same physical chemical anatomical and electrophysiologic variables are involved in both cochlear and vestibular functions The stimulus itself is different but the type of stimulus such as the relative displacement of the membranous partitions and the type of specialized structures of the cochlea and vestibule which receive it are identical In cochlea sounds in vestibule changes in position of [illegible] he body in the space are the effective stimuli Endolymph and perilymph are [illegible] sam[illegible] in the cochlea and vestibule The cupula of the ampullary cristae in the [illegible] ular canals and the otolith membrane of the maculae in utri[illegible]ule [illegible] [illegible] jelly like structures analogous to the tectorial membrane [illegible] 97 436) The properties of the vestibular neuroepithe[illegible] [illegible] ange and metabolic activity absence of affinity [illegible] ucopolysaccharides incapability of maintaining a [illegible] re dentical to those of cochlear neurosensory epi[illegible]

[illegible] rstanding of the relationships between the different anato[illegible] cal and electrochemical variables of cochlear and vestibular [illegible] iption of the *electric biopotentials of the inner ear* is given

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vestibule of an abnormal functional pattern of the autonomic nervous system. We first discussed this concept at the VIII Convention of the Societas O.R.L. Latina in Lausanne Switzerland, in 1950 in a paper reporting the results of the treatment of otosclerosis (especially the functional component of the disease) by alpha-tocopherol associated with testosterone and also in several following papers (230a-c 234 234a). According to Lawrence's concept of otosclerosis and Menière's disease, it seems unlikely that cochlear otosclerosis causes sensory neural deafness by the impairement of the blood supply to the stria vascularis. Otosclerosis in fact would affect vascular system which, according to his own studies discussed above, does not seem to be the source of nutrients to the organ of Corti. In our opinion, the primary shutdown of a number of blood vessels supplying oxygen and other vital substances to the cochlear hair cells via labyrinthine fluids would alter not only the mechanism of that supply nutrients, but also perhaps primarily the electrochemical environment formed by endolymph and perilymph which makes possible the conversion of the mechanical energy of the specific cochlear and vestibular stimuli into electric impulses. There are strong reasons for believing that the electrochemical environment (due especially to cation and protein content of labyrinthine fluids) is generated and maintained by the specialized function of the cells and the blood vessels of the stria vascularis, and secondarily by the function of other cochlear structures in which endolymph and perilymph are produced and absorbed (see Chapter II)

1 The transducer function of the hair cells of the organ of Corti is usually expressed as an alternating current discovered by the American investigators Wever and Bray (426 427) in 1930 in the cat, and called *cochlear microphonics* by the English physiologist Adrian (1) in 1931 This biopotential also known as microphonic response of the cochlea, has been extensively studied by Stevens and Davis (375) Davis and co-workers (80-85 87 88) and numerous other authors (357 434) ( )

Cochlear microphonics depend upon the integrity of the hair cells and seem to reflect at low and moderate sound intensities the instantaneous amplitude of displacement of the tectorial membrane relative to the reticular lamina of the organ of Corti. There is no true threshold no refractory period no adaptation and fatigue contrary to the action potentials of the VIIIth nerve (see below) Over a maximum (about 5 mV) the output decreases with the increase of the input. Other than the fraction depending on oxygen supply an anaerobic fraction has been recorded after death and called cochlear microphonics second (CM_2) in contrast to the aerobic cochlear microphonics first (CM_1)

Another response of the cochlea to acoustic stimulation is considered to be the so-called *summating potentials* The simplest interpretation of these biopotentials is that of an alternating current similar to cochlear microphonics but generated by the internal hair cells instead by the external hair cells which would generate cochlear microphonics (80-84 202) They have also been interpreted as positive and negative changes of the positive polarization of cochlear duct [endocochlear resting potential (see below)] and called therefore negative and positive summating potentials (80-84) They are proportional to mechanical and acoustic stimuli but the changes are unidirectional and proportional to the root mean square (RMS) acoustic pressure and not to the instantaneous displacement, like cochlear microphonics Since the positive and negative summating potentials are generated at the opposite ends of the basilar membrane, they have been related to the process of frequency discrimination (80 83 84)

A completely different class of cochlear biopotentials are the resting polarizations and the action potentials of the VIIIth nerve The *resting polarizations* include the direct current (dc) negative intracellular polarization of the hair cells and supporting cells of the organ of Corti the polarization of the nerve fibres of the cells of stria vascularis and Reissner's membrane They are similar to the resting potentials of the other body cells and range within 20-80 mV negative relative to the surrounding tissue fluid (80)

( ) The literature on cochlear microphonics and in general on electrophysiology of cochlea and vestibule reported in this monograph is indicated by the following bibliographic references 7 4, 5 33 36 37 41 48 5 -56 6 68 78-88 92, 93 101 3 1 6 17 9 122, 30- 38 49 50 63, 65 170, 178 82 82a, 184,186 97 98, 202-204, 212 3 7 243, 246 249 5 56 27 83, 286 307 308 325 3 7 330-333, 339-34 351 357-359, 375a, 377 384 387 392, 393, 397-399 4 7 425a, 426-428 430 42 434 and 435

The other type of resting polarization of the cochlea is the endocochlear (or endolymphatic) potential discovered by von Békésy in the endolymph of cochlear duct of the guinea pig in 1952 (33) and then studied by numerous authors (33 36 80 137 185 247 256 325 340 341 369) It ranges between +50 — (+120) mV (mean=+80 mV) Recently Schmidt and Fernandez (341) have classified various types of endocochlear potential according to animal species and potential sensibility to anoxia 1 a small sized (+5 — (+15) mV) anoxia-insensitive potential in cold-blooded animals such as the crocodile turtle and toad (less than +5 mV) the horned lizard and the common garted snake (+5 — (+15) mV); 2 a medium-sized (+15 — (+20) mV) anoxia sensitive potential in birds (pigeon and chicken) and 3 a large sized (+50 — (+100 mV) anoxia sensitive potential in mammals (monkey cat guinea pig opossum)

The endocochlear potential in mammals has also been described (247) to have different values according to the various turns of the cochlea. In the guinea pig the maximal value of +120 mV was recorded in the basal turn and near the round window no potential in the apical turn +90 — (+100) mV in the second turn +80 mV in the third turn According to Gisselson (137) however the endocochlear potential would be equal (+80 mV) in all turns of the cochlea in the guinea pig The same result has been obtained more recently by Kawata and coworkers (184) in that animal These authors have also shown that the endocochlear potential at every turn is not affected by the destruction of other turns The implication is that a localized impairment of the stria vascularis (which is assumed to be the site of generation and maintenance of that biopotential) for example an obstacle which prevents normal blood flow to cochlea may produce a hearing loss limited to a narrow frequency region such as C⁵ dip (183 184).

The relationships between this cochlear biopotential and the ion chemistry of labyrinthine fluids will be discussed on pages 31 34 and 37

The *action potentials of the VIIIth nerve* are similar to those of all medullated axones and express the changes of the resting nerve membrane following stimulation. An electric current is the result of stimulation. It flows momentarily along the surfaces of the membrane and excites the nerve fibre further down its length The propagation of the electrochemical impulse along the fiber membrane is assured therefore by a mechanism whose steps are the following (51 52 160 201 265) When the resting membrane of the nerve fibre (whose resting potential is negative inside and positive outside) is excited the potential reverses for a very short time (half a millisecond in large nerve fibres) The entire phase of the resting potential reversal and re-establishment represents the action potential or better the sequence of potentials completing its course within fraction of seconds In spite of the small size of cochlear nerve fibres (2.4 4 micra in diameter) the frequency of transmission of their impulses exceeds 1000 cycles per second. In the two opposite vibratory conditions of basilar membrane i e vibration at low frequencies (50-60 cps) and high frequencies (4000 cps) the action potential pattern follows that of the vibration of the basilar membrane At 4000 cps however every nerve fibre does not fire more than one of every 3 4 vibrations The

discharges transmitted through the VIIIth nerve are still synchronous because of the alternation of the different fibres which permits the firing of one or more fibres for each vibration. This does not occur above 4000 cps. Opposite to cochlear microphonics the action potentials of the VIIIth nerve obey to the "All-or-None Law" and are subject to the rules of latency and refractory time (80 92 130-132 180)

Concerning vestibular potentials it seems demonstrated, in spite of the quantitative differences of the experimental data that the endolymphatic potential is about 10 times lower in vestibule than in cochlea in the guinea pig In cochlear perilymph of the same animal the values obtained are 0 — (+5) mV in scala vestibuli and 0 in scala tympani in the perilymph of semicircular canals +1 — (+1 5 – 2) mV (see Table III).

CHAPTER II

Physical properties, chemical composition and electrophysiologic aspects of labyrinthine fluids and their significance for cochlear and vestibular functions A critical discussion and a table form presentation (Appendix)

The study of physical and chemical aspects of labyrinthine fluids dates back to the end of the eighteenth century when dead fishes of the selachian family (elasmobranchs) were extensively utilized. They offer the advantage of a cartilagineous skeleton and the *largest labyrinth among all vertebrates The problem of sampling* labyrinthine fluids in living animals without any significant contamination and in a volume large enough for microchemical analysis is certainly a complicated one. Actually by using glass capillaries 0.25-0 50 mm outside diameter it is possible to sample endolymph from the utricle (through the oval window after removal of the stapes) or cochlear duct (through the basilar membrane at the basal turn, approached via the round window) and perilymph from the scala tympani through the same round window This can be done either in living laboratory mammals (guinea pig, cat and dog among the animals most commonly used) or in the same animals shortly after death (see page 81) In humans too labyrinthine fluids can be and arebeing sampled (see below)

The first successful attempt to sample the inner ear fluids was made by the Italian physiologist Giovanni Rossi (328), in 1914. He sampled perilymph from the semicircular canals of the pigeon in order to study the viscosity of this fluid in relation to the transmission of sounds through the middle ear From 1923 through 926 another notable investigation of labyrinthine fluids was carried out by the Hungarian physiologist Szasz (380) who measured the refractive index and osmotic pressure of endolymph and perilymph in the dog In the same year a basic investigation on physics and chemistry of labyrinthine fluids was carried out by the Japanese investigator Kaeda (179) In this study the evaluation of the protein content and, for the first time, the analysis of electrolyte concentration in perilymph and endolymph were achieved. A similar study was carried out in the guinea pig nineteen years later in 1952 by a team of American investigators Smith Wu and Lowry (367 368), and by several authors thereafter (see the bibliography reported in Tables I XII).

Further basic step in the study of labyrinthine fluids is represented by the researches of the English-Belgian investigators Aldred Hallpike and Ledoux (4) These authors systematically compared the chemical composition of labyrinthine fluids with that of cerebrospinal fluid and blood serum in the cat and guinea pig in the attempt to establish the physiologic role the nature and the source of these fluids

Finally worthy of mention are the studies of Waltner and Raymond (415 416) on perilymph Wullstein Rauch and Kostlin (320 321 439) and Antonini and co-workers (18) on perilymph and endolymph sampled from humans after death or during operation for Menière s disease or otosclerosis Later on several investigators most of whom ear microsurgeons have been interested in studying the biochemical aspects of labyrinthine fluids sampled at time of surgery (120 159 320 321 334a 338a 416 438 439).

Tables I XII schematically summarize the body of information available in the literature concerning the biochemical and physical aspects of labyrinthine fluids in comparison with those of cerebrospinal fluid and blood serum

The most significant relationships between these fluid media will be discussed in the following section A large number of data concern chemical measurements after death. Unfortunately the reliability of these data at least concerning the measurement of potassium and sodium concentration (see page 96) is not enough to justify its acceptability

A) RELATIONSHIPS BETWEEN PERILYMPH AND ENDOLYMPH (PL-EL)

a) *Physical properties* — Viscosity specific weight osmotic pressure electric conductivity and biopotentials are lower in PL than in EL. Volume pressure refractive index and electric resistance are higher in PL than in EL. On the basis of these physical properties therefore no doubt exist that perilymph and endolymph are different fluids The role played by these physical properties of labyrinthine fluids in inner ear physiology in mammals as well as in lower animals is still speculative or even unknown For example the relationships between the viscosity of perilymph and the mechanics of cochlear partitions according to the "travelling wave" mechanism ( ) and those of vestibular system are unknown as

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( ) According to the *travelling wave mechanism* described by von Békésy (36) when sounds reach the inner ear producing an inward movement of the stapes and concomitantly an outward movement of the round window membrane the fluid wave causes a bulging of the basilar membrane toward the round window at the base of the cochlea no time being available for the movement of the fluid wave all the way up to the helicotrema and back. Because of the elastic tension created by the stretching of the basilar membrane fibres due to motion a new wave is formed in the opposite direction .e toward the stapes but it travel along the basilar membrane like the pressure wave does along the arterial walls The higher the frequency of the incoming sounds, the shortest the distance of the travelling wave along the basilar membrane Low frequency sounds therefore produc the largest waves These travel the entire length of the membrane before th y extinguish There is a particular amplitude pattern

yet. The higher viscosity of endolymph which is at a maximum in the elasmobranch fishes because of its high content of mucopolysaccharides may have some damping effect against too violent oscillation of endolymph and prevent the onset of eddying at physiologic flow rate (391) The different chemical nature of mucopolysaccharides is believed to be the reason why the endolymph of elasmobranchs is more viscous than that of mammals In the cod fish however the viscosity of perilymph has been found to be higher than that of endolymph. Perilymph of utricle and semicircular canals (superior part of the labyrinth in the cod-fish) appears to be more viscous than the perilymph of cochlea and saccule (inferior part of the labyrinth in the cod-fish) In the former the total mucopolysaccharide material is represented by hyaluronic acid in the latter most of mucopolysaccharides are hyaluronic acid. The importance of the viscosity of endolymph and other structures of the cochlea and vestibule such as tectorial membrane cupula and otolith membrane, that are not only bathed but also permeated by endolymph will be discussed in more detail on pages 34 36

The difference between the zero potential in PL of scala tympani and 0 — (+5) mV potential in PL of scala vestibuli and the +80 mV potential in EL of scala media (endocochlear potential) in mammals and the higher electric conductivity of EL with respect to that of PL are assumed to play a basic role in the generation and maintenance of the electrochemical environment necessary for the accomplishment of the transducer function of cochlear neuroreceptors (see pages 33 and 35)

The higher osmotic pressure of EL with respect to that of PL supports the hypothesis that EL is produced by an active process of secretion (by the cells of the stria vascularis see pages 34 and 43) and not simply by ultrafiltration through capillaries such as it appears to be in the case of perilymph (see pages 30 43 and 42).

The higher refractive index of PL with respect to that of EL (in spite of the higher viscosity of EL) may depend on the greater protein concentration in PL and the combination of protein molecules with those of certain ions (sodium, potassium calcium etc.).

b) *Chemical composition* — The content of organic substances of PL is greater than that of EL. The content of inorganic substances of PL, conversely is smaller than that of EL. Protein concentration in PL is about twice that of EL in the cat In the guinea pig, the protein content of EL is about 1/3 that of PL. In the

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of vibration of the basilar membrane for every frequency of sounds. It has been found that the vibratory pattern is located close to the helicotrema for the low frequencies (50- 00 cps) and close to the base of the cochlea for the high frequencies (8000 cps) The travelling wave mechanism, in addition to other factors, may account for the mode by which the discrimination of sound pitch is accomplished According to the duplex theory of pitch discrimination, the frequency of sounds is determined in relation to the "locus of the basilar membrane maximally excited by the sound wave. The central nervous system participates in the discrimination process after the impulses of cochlear nerve have reached the medullar nuclei. The amplitude of vibration of basilar membrane is believed to account for the loudness discrimination (36).

elasmobranch fish Acanthias vulgaris is it 50% greater than that of EL. In humans the protein concentration in PL is about three times that of PL. The total nitrogen however is slightly higher in PL than in EL in Acanthias vulgaris In the guinea pig non-protein nitrogen is represented equally in PL and EL. In mammals the protein fraction pattern of PL is different from that of EL. About 1/5 of proteins in PL is albumin In human serum conversely albumin represents 4/5 of the total protein content. In other body fluids (vitreous body for example) the concentration of albumin equals that of globulins In lower vertebrates such the elasmobranch fishes only globulins are present in EL. In PL, conversely 79% of proteins is represented by globulins the rest by albumin

The aminoacids found in perilymph are listed in Table VI They belong to the aliphatic mono- and diaminoacids whose molecular weight is the lowest and molecular constitution the simplest They also belong to the class of glycoforming aminoacids It is still unclear if the aminoacids of perilmph are circulating protein fractions or rather material expressing the local metabolism of perilymph and surrounding tissue No modification of the aminoacid pattern of perilymph has been recently demonstrated (66) to occur in guinea pigs loaded with tryptophane (not present in perilymph) or glutamic acid (present in perilymph) Conversely modifications have been shown to occur in the experiments carried out on aqueous humor which contains alanine serine, threonine and methionine The difference is the presence of glutamic acid and the absence of methionine in perilymph From what has been said the constance of the aminoacid pattern in perilymph seems to mean a precise local enzymatic balance. According to recent studies (63 65 66) a complex barrier process controlled by the vegetative servous system would exclude metallic ions and also certain free aminoacids from labyrinthine fluids especially perilymph.

The electrolyte concentration in PL of mammals equals that of EL concerning calcium magnesium and chlorine It is opposite concerning sodium and potassium ions Sodium is more concentrated in PL, potassium in EL. The concentration of sodium in PL is very close to that of potassium in EL. The concentration of sodium in EL is higher than that of potassium in PL. Sodium ions in scala tympani have been found slightly more concentrated than in scala vestibuli The opposite has been found oncerning potassium ( )

In the labyrinthine fluids of the elasmobranch fishes only the concentration of potassium is comparable to that of mammals. In fact the concentration ratios

( ) It has been also found (5 8) that the concentration of potassium ions in the scala vestibuli of the guinea pig increases two to three times only in the cochlear turn corresponding to the localization of the stimulating tone (for example the 2nd turn after 2000 cps tone presented at 140 db of intensity for 4-6 hours), while no change in the endolymph and the perilymph of scala tympani occurs. Sodium concentration, too, increased in all turns especially in the apical one. Similar results were obtained when the velocity of the ionic movement in cochlear partitions was studied It has been inferred that the two cochlear scalae may have different metabolism (5 8).

between EL and PL have been found (260) to be equal to 19 for potassium 1.05 for sodium and 1.2 for chloride in elasmobranchs and 0 1 and 0 9 for sodium and chloride respectively in mammals (260). In other words while in mammals the concentration of sodium ions in EL is lower than in PL, the chloride being nearly the same as in PL, in elasmobranchs sodium is more concentrated in EL than in PL. Therefore, the concentration of both sodium and potassium ions is greater in EL than in PL. The higher chloride concentration in EL balances the higher concentration of sodium and potassium ions The excess of chloride over sodium and potassium remains the same (260) In some elasmobranchs species, such as Cetorhinus maximus the higher potassium ratios between EL and PL were found to have the same order of magnitude, i.e., 32 than the ratios concerning mammals Labyrinthine fluids of Octopus vulgaris have been found to be essentially similar to each other and to blood serum (12). Most of the data reported above, however suggest that perilymph and endolymph are fluids of different nature and origin.

B) Relationships between perilymph and cerebrospinal fluid (PL-CSF)

a) *Physical properties* — Osmotic pressure, freezing point and refractive index are higher in PL than in CSF Electric conductivity conversely is lower in PL than in CSF These fluids therefore cannot be considered identical.

b) *Chemical composition* — The content of organic substances (proteins urea aminoacids ketoacids etc.) in PL is greater than that in CSF In the cat it is five times greater in the guinea pig and man, three times. The content of inorganic substances especially electrolytes is equal in PL and CSF except with respect to carbon dioxide the concentration of which is higher in CSF than in PL in man. A difference also exists in the concentration of aminoacids in PL and CSF of mammals In fact tryptophane is present in PL and absent in CSF Finally the activity of the enzymes phosphomonoesterase and lactic dehydrogenase is higher in PL than in CSF These facts also support the concept that PL and CSF have some similarities with each other but that are not identical. The hypothesis that PL is a dialisate of CSF seems to be incorrect. PL is more similar to blood serum than EL.

C) Relationships between perilymph and blood serum (PL-BS)

a) *Physical properties* — Osmotic pressure and refractive index are nearly the same in PL and BS

b) *Chemical composition* — The content of organic substances of PL is less than that of BS Perilymph and serum however show the same frequency dispersion concerning the concentration of glucose and cholesterol and also sodium, potassium and calcium The pattern of protein fractions and the aminoacid and ketoacid concentration is nearly the same in these fluids The aminoacids glycine and taurine however predominate in PL. Phosphomonoesterase and lactic dehydrogenase act

ivity is higher in PL than in BS. In man the content of inorganic substances is slightly higher in PL than in BS with respect to sodium ions and lower with respect to carbon dioxide and inorganic phosphorus, nearly equal concerning potassium and magnesium ions. From both physical and chemical viewpoints therefore PL and BS are very similar fluids. PL may be considered as an ultrafiltrate of BS.

D) Relationships between endolymph and cerebrospinal fluid (EL/CSF)

a) *Physical properties* — Osmotic pressure and refractive index are higher in EL than in CSF.

b) *Chemical composition* — The concentration of hydrogen ions (pH) in EL is higher than that in CSF. The content of reducing substances, conversely, is lower in EL than in CSF. Proteins and the cations calcium and magnesium have nearly the same concentration in EL and CSF. Only in the cat and in some elasmobranch fishes such as Raja clavata, Cetorhinus maximus and Scyliorhinus latican-dus chlorine content of EL appears higher than that of CSF. In teleost fishes a low concentration of sodium in EL with respect to that in CSF compensates for the high concentration of potassium. In elasmobranch fishes, conversely, a high chlorine concentration partially compensates for the excess of potassium ions (104).

E) Relationships between endolymph and blood serum (EL/BS)

a) *Physical properties* — Osmotic pressure is higher, refractive index is lower in EL than in BS.

b) *Chemical composition* — Total proteins and urea are more concentrated in EL than in BS. The enzymes phosphomonoesterase and lactic dehydrogenase are less active in EL than in BS. The concentration of potassium ions in EL is higher than in BS. Carbon dioxide concentration is higher in EL than in BS in the cat, lower in man. Inorganic phosphorus is equal in EL and BS. Therefore EL does not appear to be an ultrafiltrate of blood but rather the result of a secretory process by the specialized cells of stria vascularis assuring retention of sodium and liberation of potassium ions by a mechanism similar to that of the tubular function of the kidney (see pages 35, 41 and 42).

With respect to BS and, in general, to extracellular fluid as well, EL appears to have an opposite concentration of sodium and potassium ions but a concentration of these cations similar to that of intracellular fluid, i.e. high potassium and low sodium. EL is the only body fluid having a concentration of potassium ions close to that of intracellular fluid. Saliva has a potassium content higher, but not so much as endolymph, than the potassium content of other body fluids (18-22 mg/100 = 5.38 mEq/liter) (167, 305, 432). According to White and co-workers (432) the concentration of potassium in human saliva is [illegible]0 mg/100 ml (46.4 — 107.6 mg/[illegible]00 ml) = 19.7 mEq/liter.

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Perhaps the most outstanding feature of labyrinthine fluids from the biochemical and physiologic standpoints is the high potassium concentration of endolymph with respect to blood serum and perilymph. Labyrinthine fluids of the cephalopod, Octopus vulgaris are an exception, the electrolyte concentration in this species being nearly the same and also similar to that of blood (12). The reason is still unknown

The endolymphatic environment and the inside environment of a nerve were thought to have a point in common, namely the high concentration of potassium ions while the outside environment (in the cochlea the perilympatic space) would be characterized by an electrolyte concentration at least with respect to sodium and potassium ions opposite to that of endolymph and similar to that of blood serum and extracellular fluid A resting negative polarization in the nerve cells like in any other cell of the body is related to the ion concentration gradient on both sides of the cell membrane. The similarity between the endolymphatic environment of the cochlea and the inside of a nerve appeared also logical from the embryologic viewpoint since the organ of Corti originates from the otocyst and neural crest. However the discovery of the endocochlear (or endolymphatic) potential by von Békésy (33) in 1952 proved this similarity to be non existent since that potential is a positive resting potential with respect to the zero (or very close to zero) potential of the surrounding perilymph. Consideration must be given also to the fact that while the endolymphatic potential is greater in the cochlea than in the vestibule (about 10 times in the guinea pig, 397) the concentration of sodium and potassium ions in vestibular endolymph is the same as in cochlear endolymph (see Tables IX and X) Therefore the concentration gradient of sodium and potassium between endolymph and perilymph in the cochlear duct does not seem to be related to the potential difference between these fluids which is about + 80 mV in mammals (range. + 50 — (+120) mV) (340 341) (see page 22).

A sodium diffusion mechanism in the generation of the endocochlear potential has been discussed recently by Johnstone and co-workers (177) The authors start from the assumption that « For ionic diffusion to give rise to a large electrical difference of the polarity observed between endolymph and perilymph the interface would have to be selectively permeable to a positive ion at a relatively high concentration in perilymph or a negative ion at a relatively high concentration in endolymph The CL is unsuitable since it already is at high concentration in perilymph. The pH of both fluids is similar (for comparison see Citron et al. 1956) (70) making H OH and HCO unlikely Na remains as the most likely possible ion concerned but the sodium concentration in the scala media would have to be lower than has been reported so far The mean measured potential, 80 mV would require the scala media sodium concentration to be less than 5 mM/l the largest values reported 110 mV (203) would require it to be less than 1 7 mM/l Because the likelyhood of the contamination of samples by high Na perilymph is very great it must be assumed that the lower the Na values

obtained the less was the perilymph contamination" On the basis of their measurements (see Table IX) the authors (177) conclude that the concentration of sodium in endolymph (mean = 1.9 mM/l) is low enough to admit that the positive endocochlear potential is a sodium diffusion potential. In the discussion of their data they point out that "The lowest values obtained (1.4 mM/l) would correspond to a sodium equilibrium potential of 60 log 137/1.4 = 118 mV. Both low sodium concentration and a high relative permeability to sodium are required to generate a large potential so that a low concentration of sodium in the endolymph need not necessarily be accompanied by a large potential diffusion. A lack of differential permeability is presumed to be the reason of the low endolymphatic potential in the vestibule of the guinea pig (177). There the concentration of sodium too is low and the endolymphatic potential is only +4 mV (369). In the turtle and frog the measured endolymphatic potential is less than +5 mV (340, 341) and the measured K/Na ratios are 42 and 30. These ratios suggest a concentration of sodium in the cochlear endolymph of only 3.4 mM/liter.

Also the recent studies of Enger (104) on the electrolyte composition of labyrinthine fluids of elasmobranch and teleost fishes seem to support the hypothesis that the endolymphatic potential is independent of the different concentration of sodium and potassium ions in endolymph and perilymph. The author (104) found that the high potassium concentration in the endolymph of teleost fishes is compensated by a low sodium concentration and that the sodium concentration in the endolymph of elasmobranch fishes is equal or slightly higher than that of the cranial fluid (In teleost fishes this fluid is at the same time perilymph because the membranous labyrinth of teleosts is not enclosed in the skull or in a bony labyrinth but loosely suspended in the cranial cavity.) The concentration of chlorine conversely is higher in endolymph and more than compensates for the high potassium concentration as we said above. Enger (104) estimated by Nernst's equation the potassium equilibrium potential for teleost fishes and found that is to be +65 — 51 mV instead of the recorded potential of +8 — (+11) millivolts. The calculated sodium equilibrium potential ranges between 55-91 mV in the three species studied (Gadus morrhua, Cottus scorpius and Salmo irideus) "while the saccule potential is very close to zero millivolts. This may mean that the concentration difference of sodium ions on the two sides of the saccular membrane is balanced by the actual potential difference. In elasmobranchs the situation is reversed again, the chloride distribution would be balanced by a saccular potential of +5 mV which is close to the recorded value reported by Murray and Potts (296) (260), while sodium would be not in equilibrium since its equilibrium potential is [illegible] very close to 0 mV" (104). "It is very unlikely" therefore "that those ions are responsible for the measured potential. If they are, it would mean that the saccular potential is a sodium potential in teleosts and mammals and a chloride potential in elasmobranchs" (104). The reason why remains to be answered as well as the possibility of an active potassium transport mechanism suggested by Murray and Potts (260).

This mechanism has been taken in consideration by Rauch and co-workers

(322) in a recent study of the selective permeability of Reissner's membrane to radioactive material (see page 40). According to these authors (322) Reissner's membrane would be the site of an active transport of potassium ions from the perilymph of scala vestibuli into the endolymph of scala media against the concentration gradient. The electric potential relative to this ionic current calculated by Nernst's equation is of the same order of magnitude of the measured endocochlear potential (mean. 80 mV in mammals). Reissner's membrane would act as an insulator in preventing free diffusion of ions through the membrane and the consequent equalization of the ion concentration (322). When sounds reach the cochlea the mechanical displacement of Reissner's membrane would alter the electric field in the cochlear duct. The hairs of the hair cells acting like antennas, would record the change in the electric field like the electrodes of a nystagmograph record the variations of the electric field formed by the negative potential of the retina and the positive potential of the bulbar conjunctiva as a result of a change in position of the eyeball (322).

Several facts seem to support the hypothesis that the endocochlear potential is a sort of motor potential generated and maintained by an active process of secretion (potassium-pump mechanism) of that specialized part of the spiral ligament of the cochlear duct known as stria vascularis (because of its very rich vascular supply). This potential would be similar to the sodium potential recorded in the frog skin (401) and to the chlorine potential generated by the HCl-producing cells of the gastric mucosa (161). These facts are the following: 1. Direct measurement in the "waltzing guinea pig" which lacks of the organ of Corti has shown that the endocochlear potential is highest close to the stria vascularis. 2. The endocochlear potential suddenly drops during asphyxia because of the interruption of all metabolic activities (80). Anoxia has been produced in all structures of the cochlear duct by local injection of sodium cyanide (87) or by suspension of blood supply to (87, 116, 117, 197, 203, 292, 431) or venous return from the cochlea (88) or oxygen deficiency in the endolymph of cochlear duct by injection into scala media of a mixture of glucose and glucose-oxidase. The enzimatic oxidation of the substrate favored by the oxygen present in endolymph lowers the oxygen content of this fluid. The surrounding tissue conversely remain unaffected (246-248). 3. The *stria vascularis is a structure characterized by a very high metabolism* (80, 247, 251, 385). 4. Streptomycin poisoning and the subsequent destruction of the hair cells of the organ of Corti (precisely the outer hair cells) do not change the endocochlear potential while markedly reduce cochlear microphonic potential (88).

These data also indicate that the hair cells are not responsible for the generation of the endocochlear potential as originally thought by Ranke (311), and that this potential is strictly depending upon an oxidative metabolism in the stria vascularis. Recent studies however make questionable this conclusion because they have shown that perfusion with solutions having low oxygen tension re-establish the endocochlear potential depressed by anoxia (163).

The significance of the high potassium concentration in the endolymph and the existence in cochlear endolymph of a positive resting polarization of about 80

mV in mammals is not completely understood as yet. It is conceivable that it creates the electrochemical environment necessary for producing the extremely high sensitivity of hearing. The high voltage difference (about 170 mV) produced by the endocochlear potential (+80 mV) and the resting polarization of the hair cells of the organ of Corti (—70 mV) would lead to a constant random firing of the terminals of the VIIIth nerve. The resulting absence of inertia in an otherwise non-active system at rest may explain how an audible threshold can be produced by an amount of energy which approximates that of the amplitude of vibration of an air column equal to the diameter of a hydrogen atom (15, 36, 94) (*). The incoming sounds have only to modulate an ongoing system rather than bring it into action. Perhaps the magnitude of the endocochlear potential correlates directly with the quantity of the background (non-evoked) action potentials of the VIIIth nerve independently of the cochlear microphonic function. This hypothesis deserves attention in further studies. The existence in the vestibule of an endolymphatic potential lower than that in the cochlea (397) might simply mean that the sensitivity of the vestibular mechanism is smaller than that of the coclear mechanism, at least with respect to the role played by the endolymph potential in the process of conversion of the mechanical energy of cochlear and vestibular stimuli into electric energy.

The similarity between the order of magnitude of a hydrogen atom may account for the necessity of cochlear neuroreceptors to receive their nutrients indirectly through labyrinthine fluids (21) rather than directly via blood vessels like the neurosensory hair cells of the vestibule (62, 359, 360). A direct supply of oxygen and other nutrients from circulation would probably interfere with the hearing mechanism since movement of blood in the vessels would create noise and disturb hearing function. This noisy background would be prevented by the presence of endolymph and perilymph around the sensory neuroepithelium of the cochlea.

The complexity of the problem of the relationships between the electrolyte concentration of labyrinthine fluids and the endolymphatic potential appears still great when the relationships between the high potassium concentration in endolymph and the other important cochlear biopotential, namely cochlear microphonics, are taken in consideration.

It is known that hydratation and viscosity of colloidal systems such as the tectorial membrane in the cochlea and the cupula and otolith membrane in the vestibule depend upon the concentration of potassium ions bound to macromolecules (152) (namely the protein-bound polysaccharides in the case of the cochlear

(*) According to Towe and Rauch (396a), at the threshold of hearing the maximum displacement of the tympanic membrane approximates [illegible] of air molecules ranging from 10^{-5} cm (for low frequencies to [illegible] cps), and the amplitude of the basilar membrane [illegible] approximates 10^{-11} cm. This value is three orders of [illegible] of the hydrogen atom and only one order of [illegible] nucleus of an atom [illegible]

and vestibular gelatinous membranes described above) The concentration of potassium ions and the ratio magnesium/calcium of the tectorial membrane have been found to be very close to those of endolymph (270). The tectorial membrane may hold the positive charges of endolymph since it is negatively charged The oscillating-ion-osmotic system of tectorial membrane appears to have dimensions and velocity similar to those of the acustic wave movements (see page 34) (266). This system therefore may play a basic role in the transducer function of the hair cells i.e., the conversion of the mechanical energy of the incoming sounds into electric energy (cochlear microphonic potential) With respect to the relationships between this biopotential and the high potassium concentration in endolymph the latter may serve to maintain the appropriate viscosity of the tectorial membrane and therefore the proper amount of bending of the hairs of the hair cells (80) The relationships between the movement of the tectorial membrane and the basilar membrane would be such as to produce a shearing force and consequently varying degrees of bending of the hairs in relation to the magnitude of sound pressure Cochlear microphonics and summating potentials in Davis hypothesis (79-82) may express changes of the electric resistance in the circuit formed by the two biologic batteries i.e the endolymphatic space and the hair cells The endocochlear potential and the negative resting polarization of the hair cells would be connected in series across the hair-bearing surface of these cells. The same when stimulated would act as a variable resistance modulating the endocochlear potential (80 82-85) ( ) Any change of the potassium ion concentration

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( ) The mechano-electrical theory of hearing advanced by von Békésy (36) and Davis (80-85) perhaps does not take into proper account certain morphological and biochemical characteristics of the organ of Corti which have been described recently by the Russian investigators, Vinnikow and Titova (4). They formed the basis of the *cytochemical theory of hearing* advanced by these authors. Two important facts must be emphasized here Exposure to sounds of the organ of Corti in vivo and in vitro increases reversibly the affinity of the hair cells for vital stains, such as neutral red. This phenomenon has been interpreted by the authors (4) as indicative of a reversible denaturation of cytoplasm proteins Acetylcholinesterase is widely distributed in the cochlea, especially in stereocilia of the inner hair cells, in the hairs of the outer hair cells of the basal turn (more in the first row less in the third row). The enzyme is also found at the base of the inner hair cells and in the inner spiral bundle in the superior portion of the cochlea and at the base of the outer hair cells and in the outer spiral bundle in the inferior portion of the cochlea

From these data and from the fact demonstrated by Few (9) that cochlear microphonics increase while the action potentials of the VIIIth nerve decrease following stimulation of the efferent bundle [which is believed (345) to be formed by cholinergic fibres] the authors (4) develop cytochemical theory of hair cell excitation in which mechano-electrical and biochemical processes would relat to each other Acetylcholine (whose source in the endolymph is not identified as yet) would be converted to the stereocilia of the hair cells by the shearing movement of the endolymph. The hair cells would be then depolarized and energy released during the anaerobic phase of their metabolism involving carbohydrates. This anaerobic phase would account for the generation of cochlear microphonics. Further energy would be provided by entrance into action of the aerobic phase of hair cell metabolism which would account for the generation of the action potentials of the VIIIth nerve.

in endolymph as well as any condition able to influence the grade of polymerization or depolymerization of the mucopolysaccharides of the tectorial membrane may modify the hydration and viscosity of this membrane and consequently increase or decrease the bending of the hairs of the hair cells relative to a given sound pressure and the inherent mechanical displacement of labyrinthine fluids and cochlear partitions. An increase in stiffness of the tectorial membrane due to a reduction of the potassium ion concentration in endolymph may have the effect of decreasing cochlear microphonics and summating potentials (80 82-85).

This theory will be critically discussed below where a similar mechanism will be analyzed in relation to the process of excitation of vestibular neuroreceptors. When the German investigator Steinhausen (373) first demonstrated in 1927 that the cupula completely closed the endolymphatic canal the mechanism of stimulation of the vestibular neuroreceptors was believed to consist simply of the deflection of the ampullary cupula following endolymph displacement. The hairs of the hair cells which were thought (incorrectly see below) to be completely embedded in the jelly-like substance of the cupula would be bent in proportion to the magnitude of the endolymph displacement (123) Through the accumulation and correlation of knowledge provided by a large number of anatomical chemical and electrophysiologic investigations in the last twenty years, has a clearer picture been achieved of the mechanism by which vestibular neuroreceptors are stimulated (312)

Electronmicroscopic studies (43 110 111 168 423) have shown that the hairs of the vestibular hair cells like those of the cochlear hair cells are tube like extension of the cell membrane rather than flexible rod-shaped structures and that they are not embedded in the gelatinous substance of the cupula but arranged within it in such a way that fine canals exist between each hair and the contiguous one (43 110 111). When the tectorial membrane is not at rest, the hairs of the hair cells may not be in contact with the surrounding membrane and in any case they would be in contact with the tectorial membrane only at their tips (110). In those canals between the hairs of the hair cells fluid movement has been observed in both the opposite directions after the deflection of the cupula in the ampullo-fugal and ampullo-petal directions (96).

Chemical and physiologic studies by Dohlman and co-workers (96-99) have shown that the radioactive sulphur injected into a pigeon and detected in the semicircular canals at increasing periods of time from the injection passed into endolymph through a secretory mechanism of the vestibular epithelium and became detectable in great amount in the cupula. The highest concentration of protein-bound sulphopolysaccharides injected into the pigeon was found within the cupula Recent experiments (113) support Dohlman's hypothesis (95 96) which can be summarized ad follows When fluid moves in the fine canals surrounding the hairs in the cupula after the deflection the polysaccharide molecules enter in motion and as a result they release the positive potassium ions. This release occurs in one direction after an ampullo-fugal deflection and in the opposite direction after an ampullo-petal deflection of the cupula Thus the direction of the flow would

change the electric biopotential around the hairs of the hair cells. By assuming that the cell membrane covering the hairs is functioning as an insulator the work of the vestibular neurosensory cells may be considered as that of a condensor The positive charge of the cell membrane would change to negative or to positive if a positive or a negative charge developed in the surrounding environment

The hypothesis is also supported by the results of electrochemical studies in vitro in which the electrostatic charges of the mucopolysaccharide molecules of a substance (for example, hyaluronic acid) forced to move within a tube were investigated (68 175) The heavy and elongated macromolecules of mucopolysaccharides (averaging 0 5 micra in length and 1,000,000 in weight) are negatively charged and capable, therefore of binding a large number of potassium ions which are positively charged. By moving hyaluronic acid in a tube it has been found (68 175) that the heavy large mucopolysaccharide molecules remain behind and the smaller and lighter potassium ions move quickly in the same direction of the motion produced in the colloid The bending resulting from the heavier molecules which become adherent to the walls of the tube gives rise to a change in potential since the positive charge increases at the leading portion and decreases at the trailing part of the jelly-like substance. This type of potential is known as "displacement potential" or flow potential" (175). It is in the range of 5 100 mV between the front and the back of the colloidal substance in motion. It cannot be recorded until the gelatinous mass comes back to its starting point when the energy of the motion stored as elastic potential (i.e a potential associated with the inactive elastic substance) becomes kinetic energy within a variable period of time.

If one considers these electrochemical data in comparison with those provided by the observation of the structure of the cupula under the electron microscope (423), the mechanism by which the transducer function of the neurosensory endorgans of vestibule is accomplished may be better understood. In fact, it is in the fine canals surrounding the hairs of the vestibular hair cells that the mechanical energy of endolymph and cupula displacement is converted into electric energy

Another series of investigations which succeeded in supporting this electrochemical theory of the excitation of vestibular neuroreceptors is shown by electrophysiologic experiments Electric biopotentials have been recorded not only in vestibular endolymph and perylymph but also in cristae and cupulae of semicircular canals and maculae of utricle and saccule (101 369 397 399) By testing the horizontal canal, it was found (397) that the biopotential increases during the utriculo-fugal displacement of the cupula, and decreases during the utriculo-petal movement Opposite electric changes were recorded when the experiment was carried out in the vertical semicircular canal. It was also established that in the ampullae of semicircular canals like in the cochlea, endolymph and cupula are electropositive, while the ampullary crista its hair cells and the terminals of the vestibular nerve are electronegative.

Attempts have been made (80) to interprete the high concentration of potassium ions in endolymph and the generation of the cochlear microphonic response

on the basis of the same electrochemical mechanism of the displacement potential hypothesized for a better understanding of vestibular physiology (97) As a matter of fact, by the same type of experiments in which the electrostatic charges of the mucopolysaccharide molecules of hyaluronic acid were investigated after motion in a tube (175) the generation of a cochlear microphonic like potential by alternating pressure of tone frequency was discovered (175) Since hyaluronic acid was found in high concentration in endolymph not only in sharks and in the codfish (172 174 406) but in the guinea pig as well (69 70 304) it has been suggested that the displacement of endolymph relative to the mucopolysaccharide molecules adhering to the hair cells or the bending of their bond to the potassium ions could produce a change in the static potential of the hairs and the membrane of the hair cells and that this change in turn would represent the cochlear microphonic potential (98) However the decrease in potential during anoxia (87 116 117 203 431) or reduced blood supply to the cochlea (197 202) or following increase in potassium concentration in the perilymph of scala timpani (384) are contradictory arguments to the hypothesis that the cochlear microphonic effect originates from the displacement of endolymph relative to the mucopolysaccharide molecules of the tectorial membrane (413)

Recent histochemical studies on the structure of the tectorial membrane (270) on the other hand have not confirmed the results of the classic investigations which suggested a non-homogenous jelly like structure rich in proteins and protein-bound polysaccharides as the basic constituent of this membrane. According to a recent histochemical study by Naftalin and co-workers (270) almost all of the material of the tectorial membrane is formed by a non-collagenous protein containing disulphide linkages potassium magnesium and in smaller amount calcium ions. Only a small proportions of this material is mucopolysaccharides. We have already emphasized that morphologically the tectorial membrane is no longer considered to be a homogeneous gelatinous substance but rather as a honey comb-shaped structure formed by filaments running transversely and creating fine canals which are filled with endolymph. The mechanical properties of this membranous structure are anisotrophic i.e the elasticity of the structure is not the same in transverse and longitudinal directions (168)

* *

If one surveys the current status of knowledge concerning the relationships between the different variables of cochlear and vestibular functions hypotheses and theories appear more numerous than proved facts especially with respect to the basic problem of the role played by labyrinthine fluids in those functions. Significant facts have been provided by experiments in which the cochlear potential were recorded after having modified the chemical composition of labyrinthine fluids by intracochlear injection of solutions whose concentration in sodium and potassium resembles that of perilymph or endolymph (87 384). These experiments have

demonstrated that 1 cochlear potentials do not change following complete substitution of perilymph with a solution (for example Ringer s solution) having an electrolyte concentration similar to that of perilymph 2 cochlear microphonics and summating potentials decrease while endocochlear potential does not significantly change after injection into cochlear duct of the same Ringer s solution (i.e. a solution rich in sodium and poor in potassium ions with respect to endolymph)· 3 cochlear microphonics and summating potentials do not change following injection into cochlear duct of a salt solution having a concentration of sodium and potassium ions similar to that of endolymph 4 the action potentials of the auditory nerve and cochlear microphonics decrease rapidly while the endocochlear potential remains unchanged following injection into scala tympani of a salt solution electrolytically similar to endolymph.

These data first of all succeed in clarifying the nature of the positive endocochlear potential They prove the independence of this potential and the action potentials of the VIIIth nerve from the different concentration of sodium and potassium ions in perilymph and endolymph and from hair cells function They also indicate that the basilar membrane is permeable to ions while the reticular lamina of the organ of Corti and Reissner s membrane are not. The boundary limits of the cochlear duct on the side of scala tympani must be the reticular lamina rather than the basilar membrane The body of the hair cells and the terminals of the auditory nerve, therefore would be bathed by a fluid (perilymph or corti lymph) whose concentration in sodium and potassium ions is similar to that of extracellular fluid and therefore appropriate for the accomplishment of the electrochemical mechanism of nerve excitation. Should one of the boundary limits of scala media be the basilar membrane rather than the reticular lamina, the bare nerve endings of the auditory nerve would have as a surrounding electrochemical environment a fluid like endolymph whose ion concentration is similar to endocellular fluid. *In a fluid like this, in which the concentration of sodium is low and that* of potassium ions is high with respect to extracellular fluid and blood serum the electrochemical process of nerve excitation could not take place (386).

According to Lawrence and Clapper s studies (210), reticular lamina does not seem to be the boundary limit between endolymph in scala media and perilymph in scala tympani. By using a strong silver protein stain (Bodian s Protargol) endolymph was stained a grey color heavier than that of perilymph. Such chromatic differentiation of endolymph and perilymph whose mechanism is certainly difficult to understand, has suggested that the basilar membrane, not the reticular lamina is the boundary limit between scala media and scala tympani. The problem is still unsolved Certainly a histologic study has basic limitations where complexe mechanisms are involved such as in the cochlea and vestibule. It says nothing for example of delicate bioelectric or selective permeable properties of active membranes like those which form several regions of the membranous partitions of the labyrinth.

The tracer method has been extensively used in the past few years (5 6 28 91 140 294 300 302 322) in an attempt to give an answer to a number of still intriguing problems. One of these problems concerns the *permeability of mem*

branous labyrinth and *formation circulation and drainage of labyrinthine fluids* ( ).

Recent studies by Rauch and co-workers (322) have shown that basilar membrane is impermeable to radiosodium 24 and radiopotassium 42 injected into scala tympani and that Reissner s membrane conversely is permeable to the same tracers injected into scala vestibuli in the guinea pig This is opposite to what was found in the experiments on the effects of intracochlear injection of salt solutions on the electric potentials of the cochlea discussed on page 39 The passage of radioactive potassium in the experiments of Rauch and co-workers (322) occurs at about a five times the rate of radioactive sodium in spite of the higher concentration of potassium ions in endolymph with respect to that of the same ions in the perilymph of scala vestibuli At the same time radiosodium passes from endolymph into the perilymph of scala vestibuli at a rate equal to that of the passage of radiopotassium from perilymph into endolymph. Reissner s membrane therefore has been interpreted (322) as an electrically charged membrane The inherent ion potential generated by the active transport of ions across it (estimated by Nernst s equation to equal 80 mV) may play a part in the process of excitation of sensorial and nerve structure of the cochlea (see page 33).

The results of the experiments on intracochlear injection of salt solutions (which suggested that the walls of the membranous labyrinth are impermeable) seemed to support the longitudinal flow theory of endolymph circulation. This theory has Corti (74) as a man promulgator and was first experimentally substantiated by the classic histologic experiments of Guild (146) in 1927 They showed that Weed s prussian blue solution injected into the cochlear duct appears in the form of a precipitate in the endolymphatic sac. Guild thought therefore that endolymph circulates longitudinally along the cochlea from the stria vascularis to the endolymphatic sac. This interpretation was put in doubt by the studies of Lindsay and co-workers (221 223) and of Schuknecht and co-workers (343) which did not show appreciable changes in structure and function of the inner ear after obliteration of the endolymphatic sac in the monkey and cat Recent experiments of Lundquist and co-workers (229) further support Guild s hypothesis of endolymph circulation and absorption. Silver granules injected into scala media of the basal turn of the cochlea in the guinea pig were found in a significant amount only in the endolymphatic sac Here the epithelial cells show a marked capacity to act as macrophages with respect to silver granules

The hypothesis of a radial circulation of labyrinthine fluids was advanced by the English investigators Naftalin and Harrison (267) in 1958 on the ground of various anatomical and physiologic considerations According to these authors

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( ) The inherent literature reported in this monograph is indicated by the following bibliographic references 5 6 8- 0 3 20 28 29 44 67 91 107 134 42 146 66 169 189 192, 209d, 2 4 5 2 8 2 9 22 223, 229 243 50, 267 274 277 280 294, 300 302 322 334, 337 343-349 353 379 394, 403, 414, 418 4 9 427 and 440.

endolymph would originate from perilymph passed through Reissner's membrane Stria vascularis would "pump potassium ions into the endolymph and at the same time would absorb sodium ions in order to maintain the ion balance in scala media according to the physiologic requirements of the organ of Corti

The results of recent electronmicroscopic and electrophysiologic studies by Lawrence and co-workers (214) seem to substantiate adequately the hypothesis of the radial flow of labyrinthine fluids. These authors have described Reissner's membrane as one-to-two cells thick membrane with villous-like structures protruding along its endolymphatic surface They think, therefore that it may serve as a tissue permitting a selective diffusion affording absorption of potassium ions from endolymph and preventing the increase of their concentration in perilymph. The stria vascularis, for its part, would function not only as a site of production bu also as a site of absorption of endolymph and more specifically of the sodium ions which are in excess in the scala media following the passage of perilymph into this scala. The function of stria vascularis has been though (214) to be similar in this respect to that of renal tubules. In fact the cells of the stria the *major elements of which are facing endolymph,* have a basal plasma membrane provided with folds and protrusions especially around capillaries (362 440), which are similar to the same anatomical characteristics of the cells of the absorbing structures, such as the cells of the renal tubules mentioned before and those of the *secretory ducts of salivary glands* (*)

The electrophysiologic studies by the same authors (214) from their part have shown no marked decrease in the microphonic response of the cochlea to high frequencies over a period of four hours following rupture of Reissner's membrane

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( ) The analogy between the function of the cells of stria vascularis and those of renal tubules is also indirectly supported by the results of the treatment of Menière disease by acetazolamide (75 57 348 374 38 403) This substance is an inhibitor of the carbonic acid anhydrase, i the enzyme which catalyzes the reaction $H_2O + O_2 \rightarrow H_2CO_3$. Carbonic acid then loozes into H and HCO 3 Concerning the renal tubules, the inhibition of carbonic acid anhydrase reduces the H available so that sodium and potassium ions cannot be re-absorbed into the blood stream in form of bicarbonates Therefore they are excreted with urine the same becomes alkaline and water is eliminated from the body through an alkaline diuresis. The reduction of the available HCO^-_3 ions avoids the presence of this radical, and the electrolytes of high osmotic pressure (especially sodium) which are carried by it, from blood to the biologic fluids. A reduction of these fluids occurs and cessation of formation and a favored absoption display the therapeutic effect (local hypotension) of acetazolamide.

Most recent studies (12) suggest other explanations of the mechanism by which the effects of acetazolamide on the formation of biologic fluids occur The intravenous injection of acetazolamide in the cat has been found to decrease the concentration of potassium ions only in endolymph Since acetazolamide lowers the respiratory activity of tissues ( ) and the stria vascularis is structure having very high metabolism (64, 264, 296 4 3), it is conceivable that the reduction of potassium ions in endolymph following the administration of acetazolamide is dependent upon reduced secretory activity of the stria due to the decrease of its respiratory processes by the drug (12).

in the second turn of the guinea pig cochlea as one would expect should the flow of endolymph be longitudinal instead of radial "The changes that occur appear to be the direct result of the Reissner's membrane tear in the second turn and not a toxic effect upon the basal turn organ of Corti as perilymph move forward the basal end" (214)

Finally the experiments of Rauch and co-workers (322), too which were already discussed on page 40 seem to substantiate the radial flow of labyrinthine fluids. They demonstrated, in fact that radioactive potassium introduced into scala vestibuli of the guinea pig enters endolymph against the concentration gradient at about a five times greater than radioactive sodium. They also proved that the Naftalin and Harrison's hypothesis of an ion current through Reissner's membrane in the direction of the concentration gradient is correct post mortem too Radiopotassium ions would move from endolymph of scala media into perilymph of scala vestibuli and radiosodium ions vice versa Reissner's membrane becomes passively permeable to all ions 2 2½ minutes after guinea pig decapitation (322).

In conclusion according to the radial flow theory of labyrinthine fluids circulation the potassium concentration in endolymph would depend upon the ratio of the volume of endolymph to plasma flow through the stria vascularis per unit of time. The ion balance in scala media would be maintained by the stria vascularis which would function like the renal tubules in absorbing selectively sodium ions while pumping potassium ions into endolymph Reissner's membrane would prevent the flow of potassium ions from scala media into scala vestibuli Only a relatively slow equimolecular exchange of potassium for sodium ions would occur through this membrane

The radial flow theory of labyrinthine fluids circulation and the hypothesis that endolymph originates from perilymph passed through Reissner's membrane has suggested that perilymph rather than endolymph may be the source of nutrition for cochlear neuroreceptors (267). The nature of perilymph as a plasma ultrafiltrate formed in the perilymphatic space close to basilar membrane and Reissner's membrane seems to support this view Because of its modality of origin perilymph is certainly an oxygen-rich fluid and does not have to transverse a long distance to reach the organ of Corti if it should cross these metabolically inactive membranes According to Naftalin and Harrison (267): "This hypothesis thus takes account of the oxygen supply requires a minimum output of osmotic and ion transfer energy by the membrane cells concerned allocating the work in accordance with their anatomical structure, and in accordance with the known ion concentration gradients"

Tracers introduced parenterally and detected in the inner ear fluids have been used recently in an attempt to study dynamically intra- and extra labyrinthine barriers in spite of the criticism that such a technical approach could give rise (see page 96) One of these studies whose experimental procedure and presentation of the data is reported in more detail is that of Choo and Tabowitz (67) The authors injected radiosodium 24 and radiopotassium 42 in the form of sterile chloride isotonic solutions, into the peritoneum or the heart of the guinea pig and

sampled labyrinthine fluids at periods ranging from 2 20 hours prior to ear surgery Samples of cerebrospinal fluid aqueous humor vitreous humor and blood were also taken to establish the relative "appetite" of those body fluid compartments for the marked ions injected The concentration of sodium ions in labyrinthine fluids was found to be increased at a slower rate than in cerebrospinal fluid and aqueous and vitreous humors during the first six hours following the intraperitoneal injection of 15 25 microcuries of radiosodium 24 The concentration of the tracer was lower in endolymph than in perilymph during the first sixteen hours after the injection. Twenty four hours from the injection it equalled that of the other body fluids investigated. The concentration of radiopotassium 42 in perilymph increased rapidly fifteen hours after the administration. In endolymph it was found to equal that of blood serum within three minutes after the intracardiac injection of the tracer Between 24 48 hours it became in endolymph thirty times greater than in blood serum. It seems therefore, that sodium ions enter endolymph very slowly as compared to perilymph and the other body fluids investigated. Potassium ions on the other hand, enter faster Since radioactive potassium reaches in endolymph a concentration thirty times greater than in blood serum (this is the concentration of potassium in endolymph with respect to that in perilymph and blood serum) the authors (67) think that the stria vascularis plays a prominent role in the passage of potassium ions from blood into endolymph Concerning sodium, they believe that the passage of this ion into endolymph occurs from an independent system in the spiral ligament deriving its components from the plasma ultrafiltrated from the blood vessels of the stria vascularis The endolymph so formed would proceed through the endolymphatic system and be re-absorbed also at the lateral wall of cochlear duct. This concept of endolymph formation seems to be more in agreement with the longitudinal flow hypothesis than with the radial flow hypothesis of endolymph circulation. In Borghesan's view (44), conversely the stria vascularis would provide the cristalloid fraction of endolymph, and the vessels of the spiral prominence the plasmatic fraction. The former process would be secretory and accomplished by the specialized cells of the stria vascularis (64 205 264 353 362); the latter would be an ultrafiltration process The assumption of this hypothesis which also favors the radial flow theory of endolymph circulation is the structural inadequacy of the stria vascularis to produce entirely endolymph and on the other hand, the complete adequacy of the spiral prominence to produce the plasmatic fraction of this fluid because of the abundance and special arrangement of the blood vessels in the spiral prominence and their relationships with the terminal fibrils of the basilar membrane which fan out there (44).

The radial flow hypothesis of endolymph circulation may also be valid for the circulation of the perilymph. As a matter of fact most of the perilymph is an ultrafiltrate from the blood vessels of the perilymphatic space a smaller part deriving the passage of cerebrospinal fluid into scala tympani (166) Recent studies of Kirikae and co-workers (189) suggest that perilymph is absorbed through the perivascular spaces of the lower spiral ligament near the basilar membrane From these spaces perilymph would flow through the spaces surrounding the small ve-

nules collecting venules the posterior spiral vein and the internal auditory nerve Finally the perilymph absorbed via the perivascular spaces would reach the cerebrospinal fluid A great deal of perilymph, of course would be absorbed directly through the venous system of the perilymphatic space. In both cases perilymph flow would be radial

* *

The critical discussion of physical properties chemical composition and electrophysiologic aspects of labyrinthine fluids and their significance for cochlear and vestibular functions is now followed in the Appendix to Chapter II by a tableform presentation of the experimental data available in the literature and the inherent bibliographic references concerning the characteristics of perilymph and endolymph as compared to each other and to those of cerebrospinal fluid and blood serum in man as well as in various animal species in normal physiologic conditions

The possibility of sampling labyrinthine fluids from ears of patients affected by Meniere s disease or otosclerosis produced a certain number of data in the last few years which would need a tabulation a part. However since in that type of investigation the control situation is arbitrary and the comparison between labyrinthine fluids chemistry and that of cerebrospinal fluid and blood serum is of a limited value for testing a given hypothesis, we are not going to tabulate the inherent data and only reporting on pages 79 and 80 the conclusions drawn by the authors.

APPENDIX TO CHAPTER II

Physical properties, chemical composition and electrophysiologic aspects of labyrinthine fluids
A table-form presentation

TABLE I
LABIRYNTHINE FLUIDS
PHYSICAL PROPERTIES

VOLUME

(cu mm or lambda 1 cu mm = 0.00 ml)

ANIMAL	PERILYMPH	ENDOLYMPH	AUTHOR
Elasmobranch Fishes Scoliodontus laticaudus (After death)	Total perilymph 400	Total endolymph 200	409
	(Ratio PL/EL = 2/)		
Cat	6.77 ± .94 ( ) (N=8)	1.46 ± 1.12 ( ) (N=16)	
	(Ratio PL/EL = 4.6/)		
	24.9 ( ) SV = 5.6 ± 0.2 ST = 9.3 ± .4 (N=2)	9 ± 0.1 (**) (N=2)	***
	(Ratio $\frac{SV+ST}{SM}$ = Ratio PL/EL = 8.6/)		
Dog	78 ( ) (N=)	6 ( ) (N=2)	***
	(Ratio PL/EL = 8/)		
M n	78.3 (**) SV = 40.6 ± .4 ST = 37.7 ± 8 (N=)	.76 ± 0.1 (**) (N=)	***
	(Ratio $\frac{SV+ST}{SM}$ = Ratio PL/EL = 8.4/)		

Values indicated with one asterisk have been estimated by sampling all the perilymph (PL) and endolymph (EL) which could be extracted by means of the capillary action of glass tubing immediately after death or from the isolated petrous bone within 4-6 minutes after death. Values indicated with two asterisks have been estimated by calculating the area of cochlear partitions on histologic preparation. For the estimation of the volume of cochlear perilymph, the long and short diameters of the scala vestibuli (SV) and scala tympani (ST) were measured, and the volume calculated by multiplying π (pi) times /2 the average diameter squared times 32 mm, which is the length of the scalae. For the estimation of the volume of cochlear endolymph, the area of *scala media* (SM), as if it were triangle whose base extended from spiral ligament to internal spiral sulcus at level excluding the organ of Corti and whose height was from the same base to the point of the attachment of Reissner' membrane to the upper part of the spiral ligament, was calculated.

*** Author unpublished data.

TABLE
LABYRINTHINE
PHYSICAL
Viscosity Specific weight Pressure Osmotic

UNIT OF MEASURE	ANIMAL	PERILYMPH
		VISC
	Elasmobranch Fishes (After death)	
	1 Scoliodontus laticaudus	Lower than in Endolymph
Dyne/cm Relative to H_2O	Acanthias vulgaris	1.2
	Teleost Fishes Gadus morrhua (After death)	2
	Pigeon	1.7
Brechbuehler Units	Man	11 16
		SPECIFIC
Relative to H_2O Dyne/cm	Elasmobranch Fishes Scoliodontus laticaudus (After death)	1.0200
		PRES
mm H_2O	Cat	90-11
mm Hg	Dog	Higher than in Endolymph
	Guinea Pig	25 (9-9)
		OSMOTIC
g NaCl/100 g H_2O	Elasmobranch Fishes *Scoliodontus laticaudus* (After death)	1 131
	Cat	.046 1.006
		FREEZING
C	Elasmobranch Fishes Scoliodontus laticaudus (After death)	2.1 5
		REFRACTIVE
nD 22 C	Cat	1 33495
nD 22.5 C	Dog	3349
nD 2.5°C		335147

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1
LUIDS
ROPERTIES
ressure Freezing point Refractive Index

ENDOLYMPH	CEREBROSPINAL FLUID	BLOOD SERUM	AUTHOR
OSITY			
Higher than in Perilymph	—	—	179
2	—	—	409
1.2	—	—	174
2.9	—	—	328
6-19	—	—	438
WEIGHT			
0004	.0233	—	179
SURE			
—	—	—	1
Lower than in Perilymph	—	—	380 a
7 5 (3)	—	—	420 41
PRESSURE			
—	8	—	179
.038 .004	0 0 7 0998	—	4 2 6
POINT			
—	2 0 6	—	179
INDEX			
33435	33435	33485	
3347	3342	—	217
—	335270	—	380

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TABLE
LABYRINTHINE
PHYSICAL
Electric conductivity Electric

UNIT OF MEASURE	ANIMAL	PERILYMPH
		ELECTRIC
Reciprocal Ohm (at 22 C)	ELASMOBRANCH FISHES 1 Scoliodontus laticaudus	17.66×10^{-3}
	2. Acanthias vulgaris	20×10^{-3}
	Guinea Pig	Lower than in Endolymph
		ELECTRIC
Ohm	Guinea Pig	100,000
		ELECTRIC
mV	ELASMOBRANCH FISHES Scoliodontus laticaudus	$0 - (-4)$ (Displacement potential)
	TELEOST FISHES 1 Cyprinus carpio	—
	Cottus scorpius	—
	Lizard, Snak	—
	Crocodile, Turtle, Toad	—
	Pigeon, Chicken	—
	Monkey Cat, Opossum	—

III
FLUIDS
PROPERTIES
resistance Electric biopotentials

ENDOLYMPH	CEREBROSPINAL FLUID	BLOOD SERUM	AUTHOR
CONDUCTIVITY			
17 53 × 1	18.20×10^{-3}	—	380
22 × 10	—	—	409
Higher than in Perilymph	—	—	380
RESISTANCE			
Lower than in Perilymph	—	—	32
BIOPOTENTIALS			
−2 — (−6) (Duplacement potential))	—	—	744 0
(in saccular EL) — (+5)	—	—	180
+8 — (+) (in saccular EL)	—	—	04
+5 — (+)	—	—	340,34
+5 (or less)	—	—	
+ 5 — (+20)	—	—	
+50 — (+ ∞)	—	—	

(continued)

TABLE
LABYRINTHINE
PHYSICAL
Electric conductivity Electric

(continued)

UNIT OF MEASURE	ANIMAL	PERILYMPH
		ELECTRIC
mV	Guinea Pig	—
		—
		—
		—
		—
		—
		—
		—
		—
		—
		—
		0 — (+5) (in the PL of scala vestibuli)
		0 (in the PL of scala tympani)
		+1 — (+1.5) (in the PL of semicircular canals)
		—
		—
		—
		+1 — (+2) (in the PL of semicircular canals)

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II
LUIDS
ERTIES
resistance Electric biopotentials

ENDOLYMPH	CEREBROSPINAL FLUID	BLOOD SERUM	AUTHOR
BIOPOTENTIALS			
+50 — (+100)	—	—	341
+50 — (+80) (in cochlear EL)	—	—	32 33
+77	—	—	01
+80 (in all turns)	—	—	137
+120 (near to the round window)	—	—	247
+ 0 — (+120) (in the basal turn)	—	—	247
+90 — (+100) (in the second turn)	—	—	247
+80 in the third turn)	—	—	247
(in the apical turn)	—	—	247
+70 — (+90) (in the basal turn)	—	—	84
+60 — (+70) (in the apical turn)	—	—	184
—	—	—	80,88
+38 — (+69) (in utricular EL)	—	—	397
+43 — (+66) (in saccular EL)	—	—	397
+3 — (+54) (in the EL of the ampullae of semicircular canals)	—	—	397
+37 — (+67) (in the EL of the curvature of semicircular canals)	—	—	397
+ — (+4) (in the EL of utricle, saccule and the ampullae and curvature of semicircular canals)	—	—	101

TABLE
LABYRINTHINE
CHEMICAL
Total inorganic substances Total organic

UNIT OF MEASURE	ANIMAL	PERILYMPH
		TOTAL INORGANIC
g	Elasmobranch Fishes Scoliodontus laticaudus (After death)	7.4033
%		4.838
		1 Water-soluble
g		2.4877
%		1.625
		2. Water-insoluble
g		0.0991
%		0.064
		TOTAL ORGANIC
g	Elasmobranch Fishes Scoliodontus laticaudus (After death)	4.8165
%		3.147
		PROTEINS (Total
mg/100 ml	Elasmobranch Fishes Acanthias vulgaris (After death)	1,200
mg/100 g	Cat	268
		42
		54.40
		1.650
mg/ 00 g	Guinea Pig	50 ± 5
		75
		75
mg/dl	Rabbit	107 ± 9.4
mg/ 00 ml	Horse (After death)	291 7

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V

LUIDS

OMPOSITION

Proteins (Total Protein Nitrogen)

ENDOLYMPH	CEREBROSPINAL FLUID	BLOOD SERUM	AUTHOR
SUBSTANCES			
2.2687	6 7034	—	
4.537	4.369	—	
fraction			
1 907	2 3377	—	179
2 380	1.478	—	
fraction			
.08 9	13 5	—	
0 63	0 085	—	
SUBSTANCES			
2453	4 24 4	—	79
490	2.762	—	
Protein Nitrogen)			
800	—	—	407,411
8	31	—	7
—	5	—	69,70
—	4 75	—	4 5
—	—	6,950	58
5 ± 2	±	—	367,368
25	20	—	69,70
5	20	—	320
28 ± 4	—	—	252
—	8.2	6,9875	18

TABLE
LABYRINTHINE
CHEMICAL
Protein

SUBSTANCE	ANIMAL	PERILYMPH
Albumin	ELASMOBRANCH FISHES Acanthias vulgaris (After death)	21
	Cat	17.4
	Horse (After death)	5.05 (i.e., 280 mg/100 ml of total proteins 1,630 mg/100 ml)
	Man	—
Globulins	ELASMOBRANCH FISHES Acanthias vulgaris (After death)	79
	Cat	82.6 (i.e., 1 370 mg/100 ml of total proteins 1,650 mg/100 ml)
	Horse (After death)	48.95
	Man	—
Albumin/Globulin Ratio	Guinea Pig, Rabbit	PL < EL and BS
1. Alpha-Globulins	ELASMOBRANCH FISHES Acanthias vulgaris (After death)	7.5
Alpha-1 globulins	Horse (After death)	3.04
Alpha-2 globulins		9.4
2. Beta-Globulins	ELASMOBRANCH FISHES Acanthias vulgaris (After death)	26
3. Alpha- + Beta Globulins	Horse (After death)	24.3
	Cat	44 (i.e., 730 mg/100 ml of total proteins 1,650 mg/100 ml)
4. Gamma-Globulins	ELASMOBRANCH FISHES Acanthias vulgaris (After death)	46
	Cat	38.6 (i.e. 650 mg/100 ml of total proteins 1,650 mg/100 ml)
	Horse (After death)	10.5
Immunoelectrophoretic evidence	Man	fraction
Prealbumin and Albumin	Pigeon	fraction
Immunoelectrophoretic evidence Globulins	Man	5 fractions α_1 4 fractions α_2 5 fractions β_1 1 fraction β_2 1 fraction γ
	Pigeon	3-5 fractions including α, β_1, and-γ-globulins

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V
FLUIDS
COMPOSITION
Fractions (%)

ENDOLYMPH	CEREBROSPINAL FLUID	BLOOD SERUM	AUTHOR
0	—	—	407,41
—	—	—	58
—	49 5	50 52	8
—	—	79	407,41
00	—	—	407,41
—	—	—	58
—	50.95	49.48	8
—	—		407,41
EL > PL and BS	—	BS > EL and < EL	25
5	—	—	407,41
— —	3 6 8	3.22 9.7	8
3 5	—	—	407,41
3 5	24 6	4	8
—	—	—	58
66	—	—	407,41
—	—	—	58
8 02	4.2	2 3	8
—	fraction	—	65,66
—	—	fraction	279
—	fraction α_1 3 fractions α_2 fractions β_1 fraction β_2 fraction γ	—	65,66
—	—	2- 6 fractions inclu-ding α_1 β_1, and γ-glo-bulins	79

TABLE
LABYRINTHINE
CHEMICAL
Non-protein nitrogenated substances (Non-protein N)-

UNIT OF MEASURE AND METHOD	ANIMAL	PERILYMPH
		NON PROTEIN
mg/100 g	Cat	20
	Guinea Pig	21
		UREA
	ELASMOBRANCH FISHES (After death)	
g/g or g/2 cm³	1 Scoliodontus laticaudus	0.0297 g/2 cm³
%		1,460
mM/l		250
mM/l	2 Raja clavata	447
	Cat	11.4
	Guinea Pig	20
	Man	—
		URIC ACID
mg/ml	ELASMOBRANCH FISHES Scoliodontus laticaudus (After death)	0.072
		CREATININE
mg/50 cm³	ELASMOBRANCH FISHES Scoliodontus laticaudus (After death)	1,340
%		0.026
		AMINO
Chromatographic evidence	Horse (After death)	The same amount than in blood serum
		Glutamic acid Aspartic acid Glutamine

1 *Acta oto-laryng. Suppl.* 8

I
LUIDS
OMPOSITION
rea Uric acid Creatinine Aminoacids

ENDOLYMPH	CEREBROSPINAL FLUID	BLOOD SERUM	AUTHOR
NITROGEN			
—	20	—	69,70
21 5	21	—	
NITROGEN			
0 0252 g/g	0 044 g/ cm³	—	79
2 520	56	—	
4 0	—	—	
38	—	—	260
2 5	0.5	6 5	7
2 5		—	320
—	0-40	22 29	
NITROGEN			
9	0 143	—	79
NITROGEN			
0 384	.804	—	179
0	6	—	74
ACIDS			
—	An amount smaller than in perilymph	The same amount than in perilymph	6
—	—	—	18

(continued)

TABLE
LABYRINTHINE
CHEMICAL

(continued)

Non-protein nitrogenated substances (Non-protein N)-

METHOD	ANIMAL	PERILYMPH
		AMINO
Qualitative Chromatographic evidence	Horse (After death)	Phosphocholamine Glycine Serine Taurine Threonine Alanine Lysine Cysteine Arginine Gamma-amino-butyric acid. Proline Valine Leucine Thyrosine Phenylalanine
	Guinea Pig, Calf Man	Glutamine Glutamic acid Alanine Threonine Serine-Valine Glycocoll Leucine Aspartic acid
Qualitative Chromatographic evidence (96)	Rabbit	Histidine 4.73 Lysine 7.37 Argynine: 6.05 Asparagine and Glycine: 26.52 Glutamic acid and Threonine 14.47 Alanine 15.78 Non identified substances 25.26

I
UIDS
MPOSITION
ea Uric acid Creatinine Aminoacids

ENDOLYMPH	CEREBROSPINAL FLUID	BLOOD SERUM	AUTHOR
ACIDS			
—	—	—	8
—	—	—	65,66
—	2 78	4 71	437
—	6.08	57	
—	7 59	3-43	
—	7.2	36 7	
—	8.	3 57	
—	7 72	20.71	
—	.0	0.7	

TABLE
LABYRINTHINE
CHEMICAL
Glucose Reducing substances Ketoacids

SUBSTANCE AND UNIT OF MEASURE	ANIMAL	PERILYMPH
		GLU
g/100 ml	ELASMOBRANCH FISHES Scoliodontus laticaudus (After death)	0 029
g/l	Rabbit	1.09
		REDUCING
g/100 ml	Cat	69
		KETO
Alpha-chetoglutaric acid (gamma/100 ml)	Horse (After death)	295
Pyruvic acid (gamma/100 ml)		1130
		MUCOPOLY
) Acid mucopolysaccharides	ELASMOBRANCH FISHES Acanthias vulgaris (After death)	Absent
1 K-hyaluronate (mg/100 ml)	Guinea Pig	—
2 Hyaluronic acid	TELEOST FISHES Gadus morrhua (After death)	Present
3 Hexosamine (mg/ 00 ml)	Guinea Pig	Present 5-8
b) Sulpho-mucopolysaccharides	Pigeon	—
		ACETYL
	Pigeon	Present
		Absent
	Guinea Pig	Absent
	Cat	Absent
	Rabbit	Absent
	Man	Absent

II
LUIDS
OMPOSITION
lucopolysaccharides Acetylcholine

ENDOLYMPH	CEREBROSPINAL FLUID	BLOOD SERUM	AUTHOR
COSE ( )			
0.0 9	0 024	—	79
—	—	—	94
SUBSTANCES			
72	48	— 8	217
ACIDES			
—	0	360	7.77
—	5	300	
SACCHARIDES			
73	—	—	7 72 409.4
10- 5 (estimated)	—	—	69.70
Present	—	—	74
Present	—	—	409
5-8	—	—	69.70
Present	—	—	99 504
CHOLINE			
—	—	—	38
—	—	—	35
Absent	—	—	35
Absent	—	—	35
—	—	—	35
—	—	—	35

( ) See additional data in the Addendum on page 75

TABLE
LABYRINTHINE
CHEMICAL
Sodium Ions

ANIMAL	PERILYMPH	ENDOLYMPH
ELASMOBRANCH FISHES (After death)		
1 Scoliodontus laticaudus	5	342
Acanthias vulgaris	24	280
3 Raja clavata	8	295
	—	287
4. Cetorhinus maximus	42	273 279 (in saccular EL) 286 (In EL of semicircular canals)
TELEOST FISHES (After death)		
Gadus morrhua	—	136 ± 2.4
Cottus scorpi	—	152 ± 2 7
3. Salmo ideus	—	104
Octopus ulgar	555 ± 32	601 ± 46
Living Cat ( )	64	66
	391 5 ± 42	38 0 ± 3
Cat after death ( )	486 ± 35	40.4 ± 8
Living Dalmatian Dog	75 8 ±	—
Dalmatian Dog after death	303.6 ± 8	—
Guinea Pig	50 3	5 6- 5.8 (in utricular EL) 12 (in cochlear EL)
	148	26
	149 ± 5.4	114.6 ± 4 9
	—	.8 (1 5-2.5)
Man	38 (in PL of scala vestibuli) 14 (In PL of scala tympani)	6-18

( ) See additional data in the Addendum on page 75

1 *Acta oto-laryng S ppl. 8*

IX
FLUIDS
COMPOSITION
(mEq/l)

CEREBROSPINAL FLUID	BLOOD SERUM	AUTHOR
253	140	179
—	—	72 397
—	—	260
86	285	04
243 252	—	
93±4.0	85±7.2	
91±1.7	84±7.2	
5 ±6.6	170± 8	
—	5 5±3	12
62	55	69 70
—	—	32
—	—	
—	—	
—	—	
5	38	367 368
90	140	69 70, 32
—	—	52
—	—	77
—	—	32 438

TABLE
LABYRINTHINE
CHEMICAL
Potassium

ANIMAL	PERILYMPH	ENDOLYMPH
Elasmobranch Fishes (After death)		
1. Scoliodontus laticaudus	14	24
2. Acanthias vulgaris	37	60
3. Raja clavata	3.54	63.4
	—	58.7
4. Cetorhinus maximus	3.4, 2.7	48.0-64.0 (in saccular EL) 86.9 (in EL of semicircular canals)
Teleost Fishes (After death)		
1. Gadus morrhua	—	72.9 ± 3.2
2. Cottus scorpius	—	50.8 ± 4.9
3. Salmo irideus	—	7.9
Octopus vulgaris	7 ± 6	20 ± 3
Living cat ( )	6	117
	5.3 ± 2	107.2 ± 9
Cat after death ( )	20.7 ± 4	119.3 ± 3
Living Dalmatian Dog	7 ±	—
Dalmatian Dog after death	8.4 ±	—
Guinea Pig	4.8	44.4
	5	142
	5	142
	39.8 ± 4.6	180.7 ± 7.8
	—	151 (133-160)
Man	2.4 (in scala vestibuli) 10 (in scala tympani)	140-160

( ) *See additional data in the Addendum on page 75*

X
FLUIDS
COMPOSITION
Ions (mEq/l)

CEREBROSPINAL FLUID	BLOOD SERUM	AUTHOR
2 4	—	79
—	—	171 172
—	—	260
4.6	4 0	04
4.41 3.3	—	
3.2±0.24	3.7± .28	
3.6±0 31	3.8± .23	
5 0±1 35	.4±0.28	
—	50±	12
5 9	6.7	69, 70
—	—	32
—	—	
—	—	
—	—	
4 2	—	367 368
4	4.5	69, 70
4	4 5	321
5 9	—	35
—	—	77
5	5	3 438

TABLE
LABYRINTHINE
CHEMICAL
Chlorine Calcium

ANIMAL	PERILYMPH	ENDOLYMPH
		CHLORINE
ELASMOBRANCH FISHES (After death)		
Scoliodontus laticaudus	245	464
2. Raja clavata	321	391
	—	322
3 Cetorhinus maximus	234 239	303 334 (in saccular EL) 378 (in the EL of semicircular canals)
TELEOST FISHES (After death)		
1 Gadus morrhua	—	66±4 9
2. Cottus scorpius	—	177±4 3
3 Salmo irideus	—	—
Cat	152	158
	150	—
Guinea Pig	121 5	107
	20	11
Man	55	120-130
		CALCIUM
Guinea Pig	3± 2	3±0.2
		MAGNESIUM
Guinea Pig	2± 2	2± .2
Man	2	—

1 *Acta ot laryng S ppl* 8

FLUIDS
COMPOSITION
Magnesium Ions (mEq/)

CEREBROSPINAL FLUID	BLOOD SERUM	AUTHOR

IONS

231	—	179
—	—	260
255	240	
36 239	—	
		04
67 ± 5 5	57 ± 5	
76 ± 3.2	57 ± 5	
143 ± .2	35 ± 9	
15	—	7
50	—	69 70
22.4	93.9	367 368
22	—	69 70 32
6	0	3

IONS

3 ± 0.2	—	69 70

IONS

±	—	69 70
		321

1 *Act oto-laryng S ppl.* 8

TABLE
LABYRINTHINE
CHEMICAL
Hydrogen Ions (pH) Oxygen

UNIT OF MEASURE	ANIMAL	PERILYMPH
HYDROGEN		
	Elasmobranch Fishes (After death)	
	1 Scoliodontus laticaudus	7.41
	2. Acanthias vulgaris	6.5 6.7
	Cat	7.87
	Man	7.20
OXY		
Pressure in mm Hg	Guinea Pig	—
CARBON		
Volume per cent ( ) at t p. (0 and 760 mm Hg)	Cat	31
mEq/l	Man	10
INORGANIC		
mg/ 00 ml ( )	Elasmobranch Fishes (After death) Acanthias vulgaris	31 75
mEq/l	Man	2

( ) Conversion factor for conversion of mg/ 00 ml or vol % into mEq/l
Carbon dioxide Divide mg/ 00 ml or vol % by 22
Inorganic phosphorus Divide mg/ 00 ml by 3

XII
FLUIDS
COMPOSITION
Carbon Dioxide Inorganic Phosphorus

ENDOLYMPH	CEREBROSPINAL FLUID	BLOOD SERUM	AUTHOR

IONS (pH)

7 36	7.23	—	179
6 6 6 7	—	—	109
7.82	7.45	7 33-7.66	217
7 50	7 35	7 35	3

GEN

44-70 (close to the stria vascularis) 6- 5 (close to the organ of Corti)	—	95 (standard value)	247 248

DIOXIDE

3 5	43.2	23 75±6 5	2 7
20	8	27	32

PHOSPHORUS

75-47	—	—	7
	3	0.8- 3	32

ADDENDUM

When the typesetting of this monograph was already completed we became informed of Dr Silverstein s study of some biochemical aspects of labyrinthine fluids in the cat (355a b). In addition to the data tabulated in the Appendix to Chapter II we are reporting here the results of that study and some explanatory comments Glucose total protein lactic and malic dehydrogenase activity and sodium and potassium ions have been investigated in perilymph (PL) endolymph (EL) cerebrospinal fluid (CSF) and blood serum (BS) of the cat ante end post mortem. The results are the following

1 *Glucose* (mg%)· 66 in PL of scala tympani 70 in PL of scala vestibuli 15.2 in cochlear EL 25 1 in vestibular EL 76 in CSF 145 in BS

2 *Total protein* (mg%) 160 in PL of scala tympani 273 in PL of scala vestibuli 126 in cochlear EL 5,200 in EL of endolymphatic sac· 13 7 in CSF 7 500 in BS

3 *Lactic dehydrogenase* (International milliunits per milliliter (I.m u./ml)) 130 in PL of scala tympani 80 in PL of scala vestibuli 295 in cochlear EL 450 in vestibular EL 3 800 in EL of endolymphatic sac· 38 5 in CSF 283 in BS

4. *Malic dehydrogenase* (I.m.u./ml.)· 152 in PL of scala tympani 162 in PL of scala vestibuli 655 in cochlear EL 770 in vestibular EL 7 100 in EL of endolymphatic sac· 27 in CSF 148 in BS

5 *Sodium* (mEq/1 140 in PL of scala tympani 25 in cochlear EL 40 in vestibular EL 153 in EL of endolymphatic sac 152 in CSF 145 in BS

6 *Potassium* (mEq/1) 3 9 in PL of scala tympani 161 in cochlear EL 127 *in vestibular EL 8 in EL of endolymphatic sac· 3 6 in CSF 4 in BS*

The data show that glucose concentration is lower in El than PL, total protein markedly higher in PL than CSF lactic and malic dehydrogenase activity notably higher in EL than PL, CSF and BS There is no significant variation of the data in living cats and cats up to one hour post mortem, except for cations sodium and potassium After death the average increase of sodium is from *25 to 62* mEq/1 in cochlear EL and from 40 to 49 in vestibular EL. The average decrease of potassium is from 161 to 150 in cochlear EL. The average increase of potassium is from 127 to 143 in vestibular EL. (Perilymph cerebrospinal fluid and blood serum have not been investigated)

The low concentration of glucose in endolymph is interpreted (355b) as a reflection of the high metabolism of the stria vascularis and the organ of Corti

The high concentration of total protein, the high activity of lactic and malic dehydrogenases and the low potassium concentration in the endolymph of the endolymphatic sac are interpreted (355b) as a reflection of the filtering function of the endolymphatic sac. According to the longitudinal flow theory of endolymph circulation t is possible that the metabolites produced by the organ of Corti are

carried by the endolymph flow from the cochlear duct to the endolymphatic sac were they would be absorbed.

The fact that total protein concentration and lactic and malic dehydrogenase activity are higher in perilymph than cerebrospinal fluid is another datum in addition to several other reported in the literature which supports the concept that perilymph is essentially a blood ultrafiltrate from the capillaries of the perilymphatic space. The part played by the cerebrospinal component of perilymph seems to be unsignificant as also the histologic and physiologic experiments of surgical obstruction of the cochlear aqueducts in cat have clearly shown (344)

Relative to the only differences of labyrinthine fluids composition in the cat ante and post mortem i.e. *those concerning sodium and potassium ions* it appears that their magnitude and direction in cochlear and vestibular endolymph is not suggestive of any conclusion.

CHAPTER III

Purpose, specific aim and rationale behind our investigation of the role of labyrinthine fluids in hearing

The concept that the ear as a sensory organ works like a neural system is based only on indirect and partial evidence (see Chapter II). It depends on the fact that the electrochemical properties of labyrinthine fluids especially the electrolyte and protein concentration and the biopotentials generated by specialized structures of the cochlea and vestibule, are the properties required by the modern electric theory of nerve excitation. However no direct proof exists supporting the concept that labyrinthine fluids play a specific electrochemical role in the mechanism of excitation of cochlear and vestibular neuroreceptors No correlation study in fact, has been carried out to investigate the dynamic relationships between the chemical and electrophysiologic variables of cochleo-vestibular functions either in experimental animals or in humans affected by labyrinthine disorders. Analogously the physiologic and pathophysiologic relationships between labyrinthine fluids and the other biologic media such as cerebrospinal fluid and blood with which they may be in equilibrium are still unclear and partially unstudied as yet.

This lack of knowledge of the mechanisms of labyrinthine functions and dysfunctions and the role played by the ear fluids in assuring and maintaining these functions suggested to us a research project the general purpose of which is to answer the following questions

1 What are the dynamic relationships between perilymph and endolymph and between each one of the labyrinthine media blood and spinal fluid?

2 How vital these relationships are for maintenance of maximum intensity in hearing and equilibrium?

3 Is it possible to predict the electric activity of the cochlea, and therefore evaluate hearing from a study of the ion and protein chemistry of labyrinthine fluids first in experimental animals and then in humans at operation?

4 Is it possible to predict the chemistry of perilymph and endolymph and modify it by drugs directly or indirectly through changes in blood circulation and metabolism of tissues that are related to hearing, based upon the measurement of cochlear microphonics at the round window first in experimental animals and then in humans at operation?

5 How do the chemistry of labyrinthine fluids and the bioelectric phenomena of the cochlea and vestibule change in response to different experimental conditions to resemble those of inner ear pathology?

The relationships between such basic variables of labyrinthine functions can be studied by evaluating the physical properties chemical composition flow metabolic activities and hemocirculation involved in the production and absorption of the inner ear fluids and measuring currently the electric biopotentials of the cochlea and vestibule

The initial and fundamental step of this study is an evaluation of the dynamic relationships between the concentration of sodium and potassium ions in perilymph sampled from the round window and the cochlear microphonic potential by which the capacity of cochlea in hearing is usually expressed (41 80-84 330-333 367) This investigation has been carried out in the cat and Dalmatian dog which is congenitally deaf because of the lack of the organ of Corti Experiments have been performed in living as well as in dead animals by removing labyrinthine fluids 4-6 minutes after the animal was killed.

We developed first a technique for sampling inner ear fluids without any significant leakage or contamination and — what is most important — any disturbance of cochlear function because of the removal of fluid, and at the same time for recording cochlear microphonic potential at the round window Then a method of analysis of the microphonic function of the cochlea was developed in order to evaluate a) changes in the conductivity of sounds to the hair cells of the organ of Corti b) changes in the electric transmission from these cells to the recording electrode c) changes in the transducer function of the hair cells i e. the function by which the mechanical energy of the incoming sounds is converted into electric energy

After having established the minimum volume of perilymph necessary to produce a change in the microphonic response of the cochlea when it is removed from scala tympani the time course of this modification after first removal of fluid (considered as a control) and the relationships between the volume of perilymph withdrawn and the changes of cochlear microphonic potential we designed an experiment in which dynamic relationships between the electric response of cochlea to sounds and the concentration of sodium and potassium ions in perilymph of the first and following samples were investigated A necessary variable in this study is the withdrawal of perilymph from the round window The volume of fluid removed and the time course of the effects of this change are basic factors in determining the magnitude and direction of change of the dependent variables related to the neurosensory structure of the cochlea namely the concentration of sodium and potassium ions in perilymph During these experiments the tendency of cochlear microphonic function to recover after fluid is removed, the time elapsed after the first or repeated fluid samples and the changes in concentration of cations in perilymph were also investigated

The *rationale behind* our investigation of the relationships between ion chemistry of labyrinthine fluids and cochlear microphonic function has been critically reviewed in Chapter II of this monograph It also stems in part from

a clinical study of the effects of adrenocorticotrope hormone (ACTH) in patients affected by neurosensory hearing loss tinnitus and vertigo (234). Remission and often suppression of symptomatology following the appropriate administration of the drug were obtained and the hypothesis forwarded that the correction of ionic imbalance in labyrinthine fluids and the changes in the physical properties (depolymerization of the mucopolysaccharides of tectorial membrane) and metabolism of tissues related to cochlear function might be the reasons of the results

Another suggestive basis of the present study is the body of clinical research on the treatment of Menière s disease by a low-sodium diet or drugs able to reduce the hypertensive state of the membranous labyrinth indirectly through vasodilator and diuretic effects (129 262) It is assumed that ion and water imbalance in labyrinthine fluids is affected Menière s disease in terms of pathology is considered by most otologists to be synonym with labyrinthine dropsy (139 222 396 433) Unfortunately there are more hypotheses than facts concerning the chemistry of labyrinthine fluids in patients affected by inner ear diseases primarily Menière s disease It has been suggested for example, that vertigo may be caused by an increase in potassium concentration of vestibular endolymph (355). Similarly absence of vestibular *reactions has been thought to be related to the reduction of the* potassium ion content in the same fluid (355). It is significant that the ion balance of perilymph in patients affected by Menière s disease reveals no alteration of the concentration of sodium and potassium ions in the perilymph collected at operation (321 416 438) However appropriate sampling in such patients would de that in which is made during attacks rather than during the remission of symptoms Total protein nitrogen conversely *seems significantly increased in the perilymph* of menièric patients (164 326 416)

The hypothesis of a relationship between Menière s disease and salt metabolism would be supported if low salt intake were associated with decrease in the frequency and intensity of vertigo as it appeared from the early studies (129 262) This hypothesis does not appear to be correct however on the basis of more recent investigations. Perlman and co-workers (290) found that the frequency and intensity of the attacks of vertigo were reduced instead of increased in menièric patients in which a retention of sodium and water was provoked by administration of desoxycorticosterone (DOCA) This finding has been confirmed recently by Naftalin and Harrison (268 269) in a clinical trial in which another hormonal principle of the adrenal cortex the aldosterone was used This hormone is 25 100 times more active than DOCA in favoring the absorption of sodium in the renal tubules and 5 *times in eliminating* potassium (54 72 227 402) It was administered to menièric patients some of whom received the rest not receiving a sodium load Several attacks were observed in some patients during sodium load but not during aldosterone administration The attacks were seen in the phase of the homeostatic cycle of sodium load and excretion in which sodium diuresis took place In *spite of the maintenance of* sodium load a continuous sodium diuresis occurred A reduction in aldosterone secretion possibly attributable to sodium loading might be the cause of this effect (268 269).

the fluid was expelled from the glass tubing into a west seal plastic centrifuge tube and stored at 0°C. Figures 6 and 7 illustrate the catheter technique" on a specimen of cat temporal bone (right ear) developed for sampling perilymph and recording cochlear microphonic potential Figure 7 also illustrates the position of the capillary tubiny (0 30 mm OD) with respect of the oval window for sampling endolymph from that portion of the utricle where the openings of the superior and posterior semicircular canals are located Figure 8 shows the radiographic view of the position of the capillary tubing (replaced by a steel wire to gove contrast) introduced into the oval window for sampling endolymph from the utricle and crus commune.



Fig 2. Close-up of the round window of a living cat preparation. Note the darker aspect of the basilar membrane and the paler aspect of the bony spiral lamina of the first turn of the cochlea. The average diameter of the round window is 1 56 millimeter

The size of the tubing was chosen after experimental testing of the capillary action of tubes of varying size in the range of diameter of the round window The rate of rise of fluid is dependent upon both the pressure in the scala tympani and the capillary action of the tube Should the tube have an OD about 1 5 mm the perilymph is removed at so rapid a rate that the membranous labyrinth may be damaged Tubes of 0.40 mm OD do not appear to produce this damage as demonstrated by the finding of no change in cochlear microphonic potential during the initial active sampling with these tubes Their length averaged 7 cm so that

a larger sample being required more than one tube was used Eight to ten seconds are necessary to fill one such tube to the 5-6 cm mark.

An estimate of the volume of the fluid collected was made by multiplying the cross-sectional inside area (πr^2) by the total length of the fluid column in all the tubes filled. For these tubes the inside diameter was considered to be 50 per cent of the OD A gravimetric estimate was obtained later by weighing the total sample in the plastic centrifuge tube before chemical analysis



Fig 3. A polyethylene catheter (mm OD) is inserted into the bony ridge of the round window niche in the living cat

B) Electrophysiologic method

The function of the cochlea was studied by measuring cochlear microphonic potential at the round window in anesthetized cats and Dalmatian dogs. This potential was recorded between the active silver electrode in contact with the fluid in the polyethylene tube and an indifferent electrode placed in contact with the muscles of the neck The voltage between these electrodes is amplified 1000 fold by a Tektronix preamplifier and then delivered simultaneously to a cathode-ray oscilloscope for study of wave form and to a db root mean square (RMS) volt meter for measuring the output This meter reads 0 db for an actual signal of

1 mV at the round window The acoustic input (pure tones from 1000 to 4000 cps) was delivered from an audiometer to a 6 inches cone loudspeaker mounted in the front panel of a sound proof box in which cats or dogs were contained during the experiments. Figures 9 and 10 illustrate the equipment used in our experiments.

Three functions are involved in the mechanism of the cochlea estimated by cochlear microphonic recording. One is the mechanical transmission of the acoustic energy from the sound source all the way to the sensitive hairs of the hair cells of the organ of Corti (input or sound intensity or sound level or sound energy usually measured in db relative to 0002 dynes/square centimeter) The second



Fig. 4. The upper part of the catheter has been focused to show the electrode (OD=circa 0.35 mm) for measurement of cochlear microphonic potential and the glass capillary tubing (OD= .40 mm) for perilymph sampling in the living cat

function is the transmission of the electric signal from the reticular surface of the hair cells to the recording instrument (output or the magnitude of the alternating electric potential measured at the round or oval window and expressed as the logarythm of the voltage in db 0 db being equal to 1 volt) The third is hair cell function i.e. the release of a given amount of electric energy for a given amount of incident acoustic energy It is expressed by the ratio in per cent of the cochlear microphonic voltage increment for a given increment of sound level input.

The estimate of mechanical and electrical transmission by cochlear microphonics is dependent on the choice of zero x and y axes The zero vertical axis

or y axis is drawn at that intensity which represents the lowest (most sensitive) threshold found for that frequency in cats. At 1000 cps for example this zero vertical axis is drawn at an intensity of 20 db at 2000 cps at 16 db and at 4000 cps at 34 db The zero horizontal axis or x axis is drawn at the voltage output level which is measured with the electrodes shorted. This zero level approximates the output of a most sensitive ear receiving no sound and not acting spontaneously

The linear rising segment of cochlear microphonic curve (slope or S) is extrapolated until it crosses these two axes The sound intensity in db at which this



Fig. 5 The level of perilymph arises in the catheter after the puncture of the round window membrane in the living cat

extension crosses the zero horizontal line is indicated as MTI or Mechanical Transmission Intercept. The voltage in db at which this extension crosses the zero vertical line is indicated as ETI or Electrical Transmission Intercept By this means the effect of slope on both MTI and ETI is minimized

The values of the intercepts of the initial (control) curve are taken as zero The changes induced by further experimental procedures are expressed as differences from this zero Movement of the intercept on horizontal axis to the right expresses mechanical transmission loss [Figure 11 A) shift of MTI] and is given a negative value to the left expresses mechanical transmission gain and is given a plus value Movement of the intercept on the vertical axis downward expresses electric transmission loss [Figure 11 C) shift of ETI] and is given a negative

value· upward expresses electric transmission gain and is given a positive value Figure 12 shows the intensity functions from a representative cat in the control situation and in that which developed after perilymph withdrawal from scala tympani

This kind of view in the analysis of cochlear microphonic function is only a model to express the mechanism of the cochlea As a matter of fact while we are indicating this function by a simple mathematical relationship i e s=o/i where s=slope o=output and i=input we realize that the final effect (change of the slope or of the hair cell function) is the result of the interaction between phy



Fig 6 Specimen of the temporal bone of cat (right ear). In the foreground the round window In the background the oval window and the stapes The length of the specimen is 1 5 centimeter

sical biochemical and electric variables involved in the total picture of the cochlear mechanism as we will demonstrate According to our method of analysis, therefore slope is directly related to output and inversely related to input Thus in any of our measurements of input output and slope we would except that to maintain constant slope input and output must increase or decrease proportionately We also would expect, for a given change in slope (for example a decrease in slope) a smaller increment of output for a given increment of input (and vice versa in the case of increase in slope) For a decrease in slope input remaining con

stant we would except an increase in output of the same size Finally slope re maining constant we would expect for a given decrease of output or input that there would be a loss of input or output respectively of the same size. From what has been said we can understand how it is that we observe no relationships be tween volume of perilymph and output but still some relationships between input or slope and volume of perilymph removed or time after removal (see pages 96-98 and Table XIV). The reason for this apparent discrepancy is the complexity of the functions involved in the mechanism of the cochlea

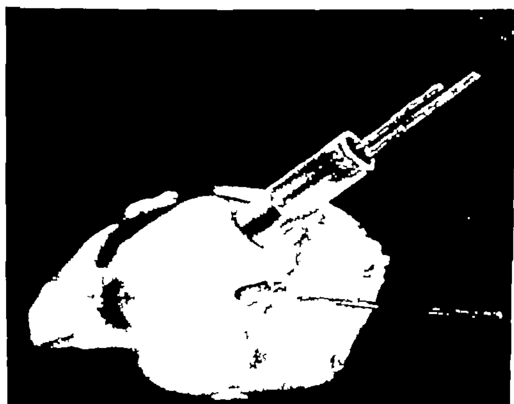


Fig. 7 The same specimen of Figure 6 but with the oval window in the foreground and the round window in the background The catheter is inserted into the round window The silver wire electrode (longer in the picture) and the glass capillary tubing (shorter in the picture) in turn are introduced into the catheter Another tubing (OD = 30 mm) is introduced into the oval window the stapes having been removed, for sampling endolymph from the utricle. The length of the specimen is 5 centimeter

C) Tracer and chemical methods

In the development of methods for the study of ion balance in labyrinthine fluids preliminary experiments employing two approaches were used microche mical and radioactive tracer

It was hoped that the latter might prove the more useful of the two through concomitant sampling of labyrinthine fluids cerebrospinal fluid aqueous humor and blood at intervals during a six hour period following the administration of the labeled ion. It was postulated that if the movement of the tracer could be followed from the blood into the other fluid compartments a comparison of per meability and secretory action of labyrinthine barriers (blood-perilymph blood endolymph cerebrospinal fluid-perilymph cerebrospinal fluid-endolymph) and the

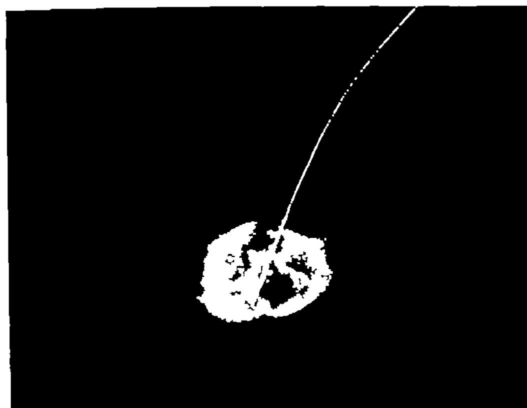


Fig. 8. Radiogram of the same specimen of Figures 6 and 7 showing the position of the glass capillary tubing (replaced by steel wire to give contrast) introduced into the oval window for sampling endolymph from the utricle. The length of the specimen is 5 centimeter

permeability of the walls of membranous labyrinth to sodium and potassium ions could be made In practice this attractive theoretical approach did not prove suc cessful for several reasons The samples of labyrinthine fluids were extremely small ranging from 0 05 4 0 cu mm and were collected in pre weight capillary tubes which were again weighed after sample collection. This necessity for a weight correction together with the small sample size was often a source of error Secondly the net counting rate of all samples except blood was extremely low To use such low counting rates would necessitate counting each sample for much longer time

periods than ordinarily employed to obtain statistically valid figures Finall in the tabulation of data where the counts per gram were expressed, an previous error would be greatly magnified by the factor used to make the necessary adjustment. Examination of the data obtained from the study of five cats ( ) led to the conclusion that microchemical methods should be used in further studies

For the microchemical study of sodium and potassium concentration in labyrinthine fluids flame spectrophotometry (11 50 1 7 23 310) was used The



Fig. 9 Equipment for the study of cochlear function by the measure of cochlear microphonic potential. 1. Cathode ray oscilloscope. Sound level meter 3 Preamplifier 4 Audiometer. 5 db meter. 6 Tape recorder 7 xy-plotter 8 Sound-proof cat box.

first step in the analytical procedure was to adjust the burner of the instrument to consume solution at the reduced rate of 2 1 2 2 ml/minute. This rate was found to be constant through the preparation of a calibration curve and the analysis of known samples During analysis of the samples the flow rate was checked frequently Since the analytical results varied widely from the accepted ratio

( ) The tracer used (radiosodium chloride) was administered intravenously t anesthetized cats of 5 kilos of average body weight t doses of 5 5 microcuries. The measure of radioactivity was carried out by gamma emission counter every hour until the sixth hour after the injection of the tracer

It was hoped that the latter might prove the more useful of the two through concomitant sampling of labyrinthine fluids cerebrospinal fluid aqueous humor and blood at intervals during a six hour period following the administration of the labeled ion It was postulated that if the movement of the tracer could be followed from the blood into the other fluid compartments a comparison of permeability and secretory action of labyrinthine barriers (blood-perilymph blood-endolymph cerebrospinal fluid-perilymph cerebrospinal fluid-endolymph) and the

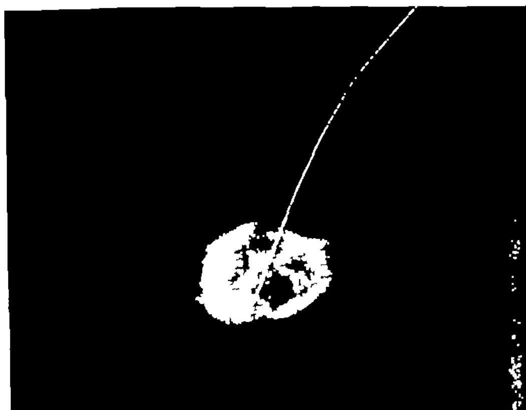


Fig. 8 Radiogram of the same specimen of Figures 6 and 7 showing the position of the glass capillary tubing (replaced by a steel wire to give contrast) introduced into the oval window for sampling endolymph from the trcle The length of the specimen is 1 5 centimeter

permeability of the walls of membranous labyrinth to sodium and potassium ions could be made In practice this attractive theoretical approach did not prove successful for several reasons The samples of labyrinthine fluids were extremely small ranging from 0 05 4.0 cu mm and were collected in pre weight capillary tubes which were again weighed after sample collection. This necessity for a weight correction together with the small sample size was often a source of error Secondly the net counting rate of all samples except blood was extremely low To use such low counting rates would necessitate counting each sample for much longer time

D) Histologic method

Histologic controls of a number of temporal bones of the cats and do under experimentation were carried out to verify any possible damage produced to the ear during surgery and technical manipulations associated with sampling of the ear fluids placement of the electrodes for measuring cochlear potentials and

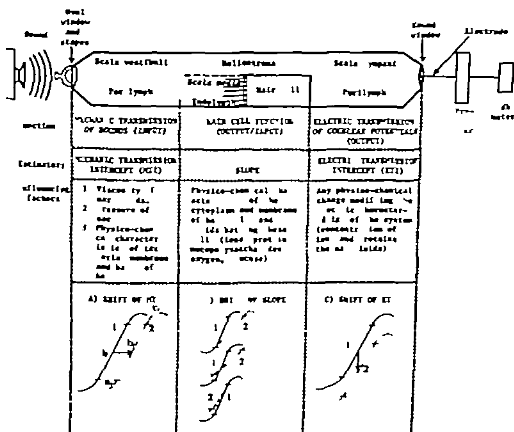


Fig. 1. Diagrammatic representation of the functions involved in the cochlear mechanism, the factors influencing these functions and the estimators of the same by recording cochlear microphonic potential. The basic types of curves expressing the microphonic function of the cochlea are also represented (=control a, b c=the three segments of cochlear microphonic curve).

so forth and also to evaluate the morphologic conditions in the cochlea of congenitally deaf Dalmatian dogs

Histologic study of the cat cochlea was also necessary to estimate the volume of cochlear partitions and therefore the volume of perilymph contained at any time in the cochlea in relation to that removed from the round window From these calculations, we then estimated the volume of perilymph which in an adult,

healthy man could be lost or sampled at operation (for example during stapes surgery) without any statistically significant disturbance of cochlear function

The specimens were fixed in 20% formalin decalcified embedded in celloidin and sectioned at 24 micra Then they were stained with Ehrlich s acid hematoxylin-eosin The decalcification of temporal bones was carried out by leaving the

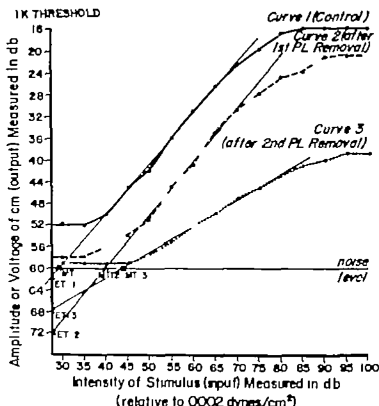


Fig 12 Intensity functions from representative cat showing the changes of mechanical transmission of sounds (input) from the sound source to the hair cells, and hair cell function (slope) after perilymph removal from the round window

specimens 5 14 days in a mixture formed by the following solutions solution A sodium citrate 50 g plus distilled water 250 ml solution B formic acid 90% 125 ml plus distilled water 125 milliliters

No perfusion technique for fixation of the specimens was used But the histologic results as compared with those obtained by this technique (165) were satisfactory enough to avoid artifacts They revealed the absence of the organ of Corti and the integrity of the stria vascularis and the nerve structures of the cochlea (see pages 107 110)

CHAPTER V

Results and discussion

The results of our investigation are grouped in two categories according t the biochemical and physiologic studies carried out

A) Biochemical Studies

Study of the concentration of sodium and potassium ions in perilymph and endolymph of cats and in perilymph of congenitally deaf Dalmatian dogs in vivo and post mortem

The results of this study are reported in Table XIII The chemical control in these experiments is represented by the first sample of perilymph taken from the round window in the living cat Its volume does not exceed 4 16 cu mm We found in fact, that a single withdrawal of perilymph greater than 4 16 cu mm or repeated samples taken within a time longer than 33 minutes from the first sample damage cochlear microphonic function and lower the concentration of sodium and potassium ions in the perilymph of scala tympani (see pages 96-100 and Table XIV).

The data reported in Table XIII demonstrate that in perilymph of living cats the concentration of sodium is 26 times greater than that of potassium, and that in endolymph the concentration of potassium is about 3 times greater than that of sodium. They also show that the concentration of sodium in perilymph is about 4 times greater than that of potassium in endolymph and about twice greater than that of potassium in perilymph.

If one considers the data of our experiments in comparison with those of the literature concerning the concentration of sodium and potassium ions in labyrinthine fluids of vertebrates one realizes that our figures are considerably higher especially concerning the concentration of sodium in perilymph of living cats. A relatively wide range of variation has been noted in the data concerning the concentration of sodium in perilymph, with respect to the concentration of potassium in both perilymph and endolymph. These values were considered normal values" in our study They could be confirmed in further experiments in which specific attention is paid to the problem of water evaporation during perilymph collection and storage before microchemical analysis. At present, however our data seem accurate enough to confirm the concept that labyrinthine fluids are opposite with

TABL

CONCENTRATION OF SODIUM AND POTASSIUM IONS (AVERAGE VALUES I
CATS AND IN COCHLEAR PERILYMPH OF CONGENITALLY

SAMPLE	Na	K	Na /K
PERI			
LIVING CATS (N=22)			
First sample (not exceeding 4.16 cu mm) (N=)	39 5±42	15 3±	6.40
Second and third samples (exceeding or not 4.16 cu mm and taken after 33 min. from the first sample) (l= 4)	280.8±49	3 0±1	21.60
Fourth to eight samples (idem than second and third samples)	258.4±60	12.8±2	20.15
LIVING DALMATIAN DOGS (N=4)			
First sample (not exceeding 4. 6 cu mm) (N=5	75 8±	10 7±	25 77
ENDO			
LIVING CATS (N= 3)			
First sample (N= 3)	38 ±3	07.2±	0 35

XIII

mEq/l) IN COCHLEAR PERILYMPH AND UTRICULAR [illegible]
DEAF DALMATIAN DOGS IN VIVO AND POST MORTEM

SAMPLE	Na	[illegible]	[illegible]
LYMPH			
CATS AFTER DEATH (N=13)			
First sample (taken within 4-6 min. after death) (N=)	48[illegible]	[illegible]	[illegible]
DALMATIAN DOGS AFTER DEATH (N=3)			
First sample (taken within 4-6 min after death) (N=3)	101[illegible]	[illegible]	[illegible]
LYMPH			
CATS AFTER DEATH (N=13)			
First sample (taken within 4-6 min after death) (N=8)	[illegible]	[illegible]	

TABLE XIV

EPSILON² CORRELATIONS RELATIVE TO 12 CATS

PREDICTION OF → FROM Y	MECHANICAL TRANSMISSION INTERCEPT (MTI) Transmission of sounds from sound source to hair cells	ELECTRIC TANSMISSION INTERCEPT (ETI) Transmission of electric potential from hair cells to recording meter	SLOPE (S) Function describing the changes of electric potential developed by hair cells in response to changes of acoustic pressure
VOLUME OF PERILYMPH First removal	No relationship	No relationship	No relationships
(.23-4 6 cu mm)	NS (—)	NS (—)	NS (—)
2 +4 K cps			Direct relation. Slope decreases as more pe rilymph is lost
Accumulated removals (up to 48 cu mm)	No relationship	No relationship	
I K cps	NS (—)	NS (—)	XXX 0.75 (0.22/ %)
TIME OF STUDY After first removal	No relationship	No relationship	No relationship
(8-33 minutes)	NS (—)	NS (—)	NS 0 3 (0.41/5%)
2, + 4 K cps			
Total after accumulated removals (up to secon hour of each experiment)	Direct relation. Conduction decreases as more perilymph is lost.	No relationship	D rect relation. Slope decreases as both total time and accumulated amount increase
I K cps	XX 0 25 (22/ %)	NS (—)	X 0.42 (0 3/5%)
VOLUME AND TIME	No relationship	No relationship	No relationship
First removal and time (0.7- cu mm/min)	NS 0 6 (0 4 /5%) Direct relation	NS (—)	NS 0 04 (0 3/5%) Direct relation. Slope decreases as both more perilymph lost and time of study is later
Accumulated removals ant total time	Input increases as both volume time increase.	No relationship	
I k cps	XX 0 2 (0 22/ %)	NS (—)	XXX .24 (22/ %)
PUNCTURE ROUND WINDOW MEMBRANE +4 k cps	NS	X 3 06 (8 / 0%)	NS

NOTE Explanation of symbols
XXX significance t better than 1% level
XX significance at % level
X significance at 5% level

changes that transpire To some extent these are opposed to each other An inspection of the individual graphs suggests that there is some tendency for the slope to recover after several of the early perilymph samples are removed but that this tendency to recover diminishes with time continued over 2 to 6 hours

9 Through this study we have found an absence of relationships between ETI and either *volume of perilymph removed time after first removal* or *accumulated removals* This implies that within the range of variation of our studies the electric transmission in perilymph (ETI) is not detectably modified by these experimental factors

10 The only significant relationship between *puncture of the membrane of the round window* and cochlear function appears to be that with the ETI The puncture of the round window membrane has been found to decrease the transmission of the electric energy from the hair cells to the recording electrode. Figure 13 shows the intensity functions from a representative cat in the control situation and in that which developed after puncture of round window membrane without any perilymph loss. We expected that the puncture of that membrane might increase the transmission of the electric energy in perilymph by reducing the re

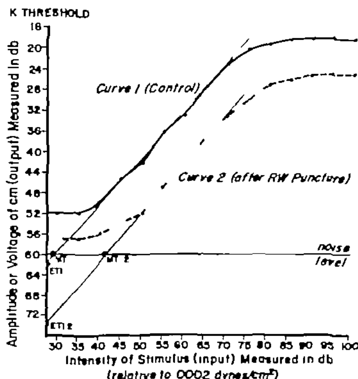


Fig 3. Intensity functions from representative cat showing the changes of electric transmission (output) from the hair cells to the recording meter after puncture of round window membrane MTI = Mechanical Transmission Intercept ETI = Electric Transmission Intercept.

distance between the electrode and the hair cells We also expected it might modify mechanical transmission by the loss of elasticity of round window membrane, thereby changing the vibration pattern of the cochlear partitions The results of our experiments however revealed no significant effect on mechanical transmission resulting from the puncture. Therefore this effect if it exists is too small to be detected by our methods. Transmission of electric energy in perilymph was decreased, but this is opposite from the expected direction We can only explain this discrepancy by admitting that round window membrane is not an element of simple resistance in the circuit A more complex picture of its role is readily possible, but hardly worthwhile to speculate about at this time.

A change in slope would imply a change in the function of the hair cells. We would not expect this effect from the puncture of the round window membrane, and in fact, no such change was detected by our methods.

The cats on which these experiments were carried out were also used to estimate the *total volume of perilymph and endolymph contained in the cochlea* In one method of estimation based on direct sampling, all perilymph and endolymph which would be removed by capillary action of the glass tubing immediately after death or from the petrous bone isolated within 4-6 minutes after death was taken. Perilymph was sampled from the round window and endolymph from the utricle approached through the oval window (Figures 2-8)

The other estimation of the volume of cochlear perilymph was based on measuring the long and short diameters of scalae vestibuli and tympani of two cats and multiplying π (pi) times 1/2 the average diameter squared times 32 mm which is the length of the cochlear scalae. The volume of cochlear endolymph was calculated by measuring the area of the scala media as if it were a triangle whose base extended from spiral ligament to internal spiral sulcus at a level excluding the organ of Corti and whose height was from the same base to the point of attachment of Reissner's membrane to the upper part of the spiral ligament. These measurements resulted in the values given in Table XV

*

The effect of perilymph loss upon the electric activity of the ear in laboratory animals (cat) was studied by Gulick and co-workers (150) in 1962 The results of our study concerning the same problem cannot be compared with theirs because of several important differences especially with respect to basic definitions. The main one is their use of the word "decreased slope to signify "parallel shifts in intensity functions" (see Figure 3 on page 579 and relative comments on page 584 in their paper) whereas we use slope as a measure of the angle that the linear function makes with the x axis. This leads to confusion between us about their meaning of "output" (see pages 84-86)

The electrophysiologic consequences of round window injury were investigated by Simmons and co-workers (358) in 1962 These authors attempt an analysis of cochlear microphonics input-output function of the same type that we are de-

TABLE XV

ESTIMATION OF PERILYMPH AND ENDOLYMPH VOLUME IN CAT AND MAN

SUBJECT	FLUID (cu mm)	METHODS OF ESTIMATION: Withdrawal of fluid from total labyrinth	METHODS OF ESTIMATION: Calculation of the area of cochlear partitions ( )
Cat	Perilymph (PL)	6 77 ± 1 94 cu mm (N = 8)	SV = 5.6 ± 0 cu mm ST = 9 3 ± 0.4 cu mm TOT = 24 9 cu mm (N =)
	Endolymph (EL)	.46 2 cu mm (N = 6)	SM = 2.9 ± 0.1 cu mm (N =)
Cat ratio	PL/EL	4 6/	8 6/
Man	Perilymph (PL)	—	SV = 40 6 ± 0.4 cu mm ST = 37 7 ± .8 cu mm TOT = 78 3 cu mm (N =)
	Endolymph (EL)	—	SM = 2.76 ± 0. cu mm (N =)
Man ratio	PL/EL	—	8.4/

( ) SV = scala vestibuli. ST = scala tympani. SM = scala media. TOT = total = SV + ST

scribing here. However they do not consider the possibility of change in slope. This difference we cannot account for because we did find change in slope in our acute cat experiments It may be that the slope change is related to more drastic alterations within the ear fluids than occur with the simple puncture of the round window membrane.

The asymptote at the top part of these curves which is reported by all observers deserves particular attention This is supposedly the result of some non-linear responses in the ear at high intensities of incident sounds (80-82 84) When non-linearity does not appear at intense sound levels then either the acoustic energy does not reach the mechanism displaying non-linearity at sufficient intensity or the mechanism is operating at a maximum We doubt that the severe loss of mechanical transmission of sounds occurs in the drum ossicles oval window or basilar membrane structures They should display the same vibrating pattern during these experiments The loss of non-linearity is then more likey to occur because of changes in the fluids tectorial membrane or the hairs of the hair cells This argument suggests that the non-linearity is most probably a function of the relation between hairs hair cells and tectorial membrane

2 *Study of the dynamic relationships between concentration of sodium and potassium ions in perilymph and cochlear microphonic function in the cat after first and further samples of perilymph*

In these experiments the control situation is that in which the first sample of perilymph is taken from the round window in a volume exceeding 4 16 cubic millimeters At this time (zero time) cochlear microphonic potential was recorded at the round window Further measurements were made immediately after the following withdrawals of perilymph. The volume of these further samples ranged between 1 33 27 88 cu millimeters The maximum time within which the following samples were taken was 4-6 hours with an average of 3 5 hours The reason of the order of magnitude of the first sample of perilymph considered as a control is in the results of our study described on page 96 and following We demonstrated that when a perilymph sample does not exceed 4 16 cu mm there is no statistically significant evidence that the withdrawal of perilymph changes cochlear function. Since in the experiments reported in this section the purpose was to study how ion chemistry of perilymph and cochlear microphonic function relate to each other in a situation of disturbed cochlear function by perilymph withdrawal we removed more than 4 16 cu mm in the first sample in order to disturb cochlear function with certainty

Examination of the data reported in Table XVI reveals that the dilution of sodium and potassium ions in perilymph samples taken after the first withdrawal directly relates to the decrease in the mechanical transmission of sounds and so in the transducer function of the hair cells Electric transmission in perilymph is slightly decreased However since the statistical analysis of the data of the experiments reported on page 96 and following revealed no significant

relationships between perilymph withdrawal and electric transmission we must assume in these further experiments that partial removal of perilymph from the cochlea does not produce a statistically significant change of electric transm ion and therefore that no relationships exist between the dilution of sodium and potassium ions in perilymph after the withdrawals and the tran miss on t th electric energy from the hair cells to the recording electrode Study of the rati sodium/potassium shows that sodium ions were diluted more than potassium i ons This confirms the results of the experiments described on pages 93 and ,6 and in Table XIII

The proved existence of dynamic relationships between the concentration of sodium and potassium ions in perilymph and both the mechanical transmission of sounds in this fluid (indicated as mechanical transmission intercept or MTI) and the transducer function of hair cells (indicated as slope or S of cochlear microphonic curve) suggests some explanatory comments on the probable mechanism by which labyrinthine fluids operate in the process of hearing through their phy sical and electrochemical properties

The results of our experiments have shown that the dilution of both sodium and potassium ions following perilymph withdrawal directly relates to decrease of MTI 2 decrease of ETI 3 decrease of S We anticipated that the decrease in sodium and potassium concentration of perilymph would have no effect on the mechanical transmission of sounds The discrepancy may be apparent only as be shown through the discussion of the mechanism by which the change in electric transmission occurs after partial withdrawal of perilymph from the cochlea (see below).

Concerning the relationships between the change in electric transmission in perilymph and the dilution of sodium and potassium ions in this fluid is clear from our data that perilymph witdrawal and its subsequent dilution are directly related to the decrease in ETI When a fluid such as perilymph loses a certain amount of cations it also loses a certain amount of electric conductivity ( )

Since the statistical analysis of the data concerning the dynamic relationships between perilymph removal and cochlear microphonic function (described on page 96 and following) did not show any significant relationship between perilymph removal and electric transmission we have now to consider the mechanism by which these phenomena may occur

When perilymph is partially removed from the cochlea through the round window the fall in pressure in scala tympani may cause an engorgement of capillary vessels and increase in their permeability such occurs in the anterior chamber

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( ) W has already emphasized the fact demonstrated in recent tudies (76) that the endocochlear potential decreases and begins to be negative after oxygen deprivation and that in this condition, which theoretically mus be concomitant with lower potassium concentration in endolymph the conductance withi the scala media decreases

TABLE

DYNAMIC RELATIONSHIPS BETWEEN CONCENTRATION OF SODIUM AND
IN THE CAT AFTER FIRST AND

Controls of chemical data are those relative to the first sample of perilymph. Controls of
Negative values express loss positive values gain (in db for mechanical transmission intercept
hair cell microphonic

CAT (No.)	VOLUME OF PERILYMPH REMOVED (cu mm)	TIME AFTER REMOVAL (hours)	Na+ (mEq/l)	K (mEq/l)	Na+/K (mEq/l)
0 658	4 20 (1st sample)	0	415.4	5.9	61
	1 51 (2nd sample)	1.05	227 3	10.6	2 4
02143	8.09 (1st sample)	0	427 9	4 4	97
	27 88 (2nd sample)	0	248.0	11.2	2.2
03271	5.23 (st sample)	0	390 4	13.8	2.82
	4.55 (3rd sample)	3.10	229.0	1 9	2.1
01419	4 61 (1st sample)	0	430.2	14.6	2.93
	1 33 (4th sample)	3.45	2 5 5	11.4	1.88
02990	25 93 (1st sample)		4 4.6	5.0	2 77
	75 (5th sample)	2.50	203 2	1 5	1.92
0 927	4.73 (st sample)	0	389 5	16 7	2.33
	35 (7th sample)	4 3	38 7	.2	1.15

POTASSIUM IONS IN PERILYMPH AND COCHLEAR MICROPHO[illegible] FURTHER SAMPLES OF PERILYMPH

electrophysiologic data are those recorded immediately after the fir[illegible] or MTI and for electric transmission intercept or ETI (in per cent of slope [illegible] input-output function).

COCHLEAR MICROPHONIC POTENTIAL								
1000 cps			2000 cps			[illegible] cps		
MTI (db)	ETI (db)	S (%)	MTI (db)	ETI (db)	S (%)	MTI (%)	ETI (%)	S (%)
−5	−6	0	−5	−5	0	—	+2	—
−12	−2	−3	−5	−6	−7	−37	−5	−34
−7	−8	−5	—	−12	+7	−7	−7	
−8	—	−5	−2	−2	−8	—	−14	—
−6	—	−15	−0	−6	—	−6	−5	−5
−1	−3	−32	−6	−7	−40	−5	−1	−5
−2	−5	—	−3	−3	−6	−9	—	−50
−5	−9	−30	−1	−2	−1	−1	−30	−57
−2	−4	+4	−3	−3	—	−5	−5	−13
−8	+	+22	−4	−9	−30	−2	−6	−29
—	—	−7	−8	−8	0	−2	−9	−4
−6	−8	−7	−18	−8	−7	−25	−2	−30

of the eye after paracentesis and partial removal of aqueous humor (89) It is conceivable that in such a condition proteins leak through the distended capillary walls This is what has been demonstrated to occur in the eye soon after the withdrawal of aqueous humor the reformed fluid having been found to be richer in proteins than the original aqueous humor before the removal (89) Should the same phenomenon occur in perilymph after its partial withdrawal an elevation of protein concentration in perilymph should increase the viscosity of this fluid Such an effect may cancel partially that of perilymph dilution with water The mechanical transmission of sounds in perilymph could be more reduced by the elevation of proteins in perilymph than increased by the dilution with water Since such a dilution lowers the cation concentration and this factor works in a direction (decrease in the transmission of electric energy) opposite to that of the increased number of the available negative charges of proteins leaked from the blood vessels (increase in the transmission of the electric energy) no change would occur if the order of magnitude of the two factors is the same This influence is compatible with the results of our experiments The transmission of electric energy in perilymph was not significantly modified by the partial removal of this fluid and consequent cation dilution.

Critical analysis of this logic compared with the results of recent experiments reported in the literature suggests that the problem is more complicated Wrba and co-workers (437) in fact have found about half of the concentration of free aminoacids in the second sample of perilymph taken from the cochlea in the rabbit with respect to that of the first sample They have found in other words a dilution of free aminoacids in the second fraction (sample) of perilymph However it is possible to consider a combination of two phenomena namely the dilution of free aminoacids demonstrated by these authors and the leakage of protein molecules from capillaries taken into consideration by us on the basis of the results of our experiments Wrba and co-workers (437) have also found that alanine asparagine, glycine and a non-identifiable substance are more concentrated in the second sample of perilymph than in the first as well as in cerebrospinal fluid and blood serum samples These data agree with our interpretation of the present data Further experiments are needed to clarify the problem and prove the point, however

By considering now the increase in protein concentration in perilymph following partial removal of this fluid from the cochlea, in relation to the transducer function of the hair cells [expressed by the slope (S) of cochlear microphonic curve] we think that *protein increase should improve this function and so increase the efficiency of the slope* The fact shown by our experiments that hair cell function not only does not increase but indeed it decreases in relation to the volume of perilymph removed time after the first removal and dilution of sodium and potassium in perilymph may be explained by an ion imbalance arising in endolymph as a consequence of that which first occurred in perilymph. When the dilution of perilymph is considered in relation to the transducer function of the hair cells, it appears conceivable that the concentration of sodium ions increases in perilymph in the initial phase of the disturbance caused by perilymph removal

Most of the dilution with water would occur at that time Finally when the concentration of both sodium and potassium ions in perilymph tend to recover further impairment of hair cell function may be related to the passage of potassium ions from endolymph into perilymph This would reduce the endolymphatic potential and so cause further progressive deterioration of cochlear function. The hypothesis of the passage of potassium ions from endolymph to perilymph may be supported by the results of our experiments We have found in fact that the dilution of potassium is less than that of sodium ions The potassium ion leakage however is not great enough to cancel the picture of the dilution of this cation in perilymph

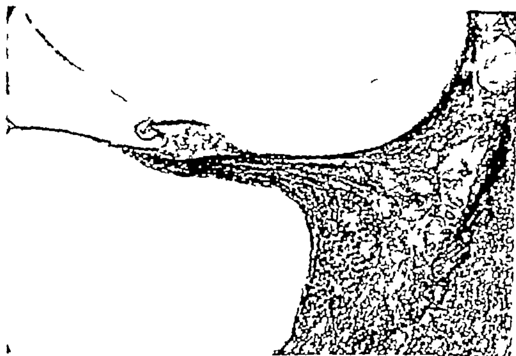


Fig 14 Histologic aspect of the cochlea (basal turn) in a two year old Dalmatian dog. The organ of Corti is absent Normal appearance of the spiral ganglion Hematoxylin-eosin 160 ×

3 *Study of the dynamic relationships between concentration of sodium and potassium ions in perilymph cochlear microphonic function and structure of the cochlea in congenitally deaf Dalmatian dogs*

The results of this study have shown that the cochlea of about 2 years old Dalmatian dogs has no organ of Corti (Figures 14 17) and that it is perfectly normal in all other respects *Since the hair cells of this organ are the site of generation of cochlear microphonic potential it is logical that in our experiments no* microphonic response of the cochlea was recorded to sounds of any frequency and

intensity ( ) Considering the concentration of sodium and potassium ions of the first sample of perilymph, it is evident that the concentration of these cations in the perilymph of living Dalmatian dogs is closer to that of the diluted perilymph of second and third samples in living cats than it is that from cats shortly after death (see also Table XIII)

Deafness and death therefore at least in our experiments seem to change the concentration of both sodium and potassium ions of perilymph in opposite ways deafness decreases it, death increases it Deafness as a function however may increase with either increase or decrease of sodium and potassium in laby-



Fig. 5 Detail of the inner portion of the basilar membrane in two year old Dalmatian dog (middle turn of the cochlea) showing complete absence of the organ of Corti. Hematoxylin-eosin. 400 X

rinthine fluids according to the results of the experiments on intracochlear injection of salt solutions discussed on page 39 The fact that the concentration of potassium ions in the perylmph of living Dalmatian dogs is less than that of sodium ions may be related to the loss of the hair cells and supporting cells in

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( ) Cochlear microphonic potential was recorded in Dalmatian dogs by the same technique used in cats (see pages 83-87)

the organ of Corti. Such an assumption suggests that a partial provision of potassium ions to labyrinthine fluids is assured by these cells. Electromicroscopic study of the cuticle-free surface of the hair cells reveals balloon-shaped protuberances (110). Potassium ions may diffuse into endolymph through such elements during the excitatory process of the hair cells (151). Hensen's and Claudius cells exhibit finger-like protrusions directed toward the endolymph also (109). Therefore, the supporting cells too may cooperate with the hair cells in producing potassium ions and releasing them into endolymph (151). If these conclusions



Fig. 6 No evidence of hair cells and supporting cells in the cochlea (middle turn) of three year old Dalmatian dog. The tectorial membrane appears collapsed on the basilar membrane. No appreciable alteration of the fibres of cochlear nerve within the osseous spiral lamina. Hematoxylin-eosin. 400 ×

stand it would appear that in Dalmatian dogs which lack the organ of Corti and the stria vascularis is normal, the greater dilution of potassium ions in perilymph with respect to that of sodium ions, as seen in our experiments, is related to the absence of the organ of Corti.

The fact demonstrated by our histologic study that the stria vascularis appears to be normal in adult Dalmatian dogs represents a matter of disagreement with the results of the most recent studies of the cochlea of these dogs (165). Hudson and co-workers (165) in fact, say that the alterations of the cochlea of Dalmatian dogs consists basically of degenerative processes involving both the organ of Corti

and stria vascularis and not the nerve cells of the ganglion of Corti and the terminal fibres of the auditory nerve (230 323) We too did not find any alteration in the nerve structures of the cochlea of Dalmatian dogs (Figures 14 and 17) Since the four animals examined were adult age does not seem a factor of disagreement between the results of our study and those of the authors mentioned above (165 230 323) Also from the published photomicrographs of the stria vascularis of the two 8 weeks old Dalmatian dogs reported by Hudson and co-workers (165) one cannot say as the authors do that the stria vascularis is either degenerated or atrophic

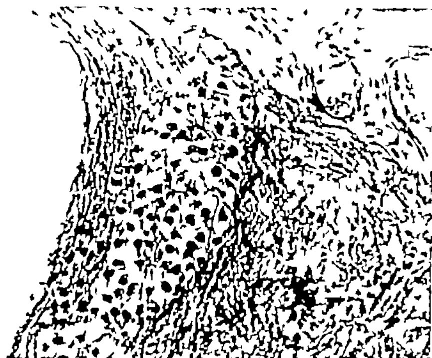


Fig 7 Detail of the spiral ganglion of a two year old Dalmatian dog whose cochlea was shown in *Figure 14* Nerve cells ppear normal Hematoxylin-eosin 400 ×

CHAPTER VI

Conclusions and implications in clinical otology

Quite apart from the specific conclusions and general assumptions made from the results of our experiments through the preceding text, one concept must be emphasized as the basic achievement of these studies on the role of labyrinthine fluids in hearing. The type and magnitude of disturbance of cochlear function caused by partial removal of perilymph from the round window in the cat and the demonstration of the dynamic balanced relationships between certain chemical electrophysiologic and morphologic key variables of cochlear function in cats with normal hearing and in congenitally deaf Dalmatian dogs point in one direction. Perilymph and we may assume endolymph, are not only nutrient fluid media and transmitters of the mechanical energy of sounds but also — and we think primarily — an electrochemical and physicochemical environment necessary for the accomplishment of the excitatory process of labyrinthine neuroreceptors. As a consequence of the partial removal of perilymph from the cochlea not only the transducer function of the hair cells but also the transmission of the mechanical energy of sounds in perilymph is basically disturbed

The results of present studies may open avenues to new investigations of cochlear and vestibular functions. This hopefully may contribute to a better understanding of several diseases of the inner ear. Correlations of the type carried out in our study may be used for example, to investigate the dynamic relationships between ion balance and protein chemistry of labyrinthine fluids and the various cochlear and vestibular potentials. We have discussed the relationships between endocochlear potential and the action potentials of the VIIIth nerve and the probable independence of the former from cochlear microphonic function. This view may be tested by designing an experiment in which a disturbance of cochlear function is produced by partial removal of perilymph from the cochlea or by injection into the blood stream of substances capable of modifying one or more variables of cochlear function. The use of certain substances in a correlation study between chemical and electrophysiologic variables may be valuable also for altering the chemistry of the inner ear fluids directly or indirectly by way of the blood stream, or changing the metabolism of the tissues of the labyrinth which are concerned with hearing and equilibrium. By understanding the reliability of predicting electric activity of the cochlea from measurement of perilymph chemistry one can estimate from this measure the hearing capacity of cochlea. Moreover by knowing the predictive reliability of perilymph chemistry from measurement of the electric energy produced in the

Summary

1 The concentration of sodium and potassium ions in perilymph and endolymph of normal cats and in perilymph of congenitally deaf Dalmatian dogs was measured by flame spectrophotometry in vivo and post mortem

2 The concentration of these cations in perilymph samples taken after the first withdrawal is lower than the concentration of the same cations in the perilymph of the first sample (which does not exceed the control 4 16 cu mm). This indicates that dilution of sodium and potassium ions occurs in perilymph after the first withdrawal From the study of the ratio sodium/potassium it appears that sodium ions were diluted more than potassium ions.

3 The concentration of sodium and potassium especially the latter in perilymph and endolymph of normal cats and in perilymph of congenitally deaf Dalmatian dogs appears to be higher post mortem than in vivo This indicates that both sodium and potassium ions especially potassium ions are released into labyrinthine fluids when cells are no longer alive. The implication is that samples of perilymph and endolymph taken even within 4-6 minutes after death are not valuable for studying problems related to their electrochemical properties and activities in the inner ear

4 For sampling perilymph from the round window a technique has been developed that prevents leakage and contamination of the fluid and which permits cochlear microphonic recording as well during sampling ("catheter technique") Endolymph was sampled from the utricle through the oval window and from the cochlear duct of the basal turn through the basilar membrane approached via round window

5 Dynamic relationships have been discovered between volume of perilymph removed (first sample) time after the first sampling and cochlear microphonic function

The results of this study demonstrate that perilymph removal from round window in the cat disturbs cochlear function by decreasing the mechanical transmission of sounds in perilymph and the release of the electric energy from the hair cells of the organ of Corti. This disturbance occurs only if the volume of perilymph removed is greater than 4 16 cu mm and the time after the first withdrawal is longer than 33 minutes Time elapsed in the experiment is more effective than volume of fluid removed in disturbing mechanical transmission of sounds volume is more effective than time in disturbing hair cell function. The simple puncture of the round window membrane i.e *without any leakage of perilymph from* the same decreases only the electric transmission from the hair cells to the recording electrode

6 Dynamic relationships have been discovered between the concentration of sodium and potassium ions in perilymph sampled at the round window in the cat

and cochlear microphonic potential recorded at the same window The dilution of sodium and potassium ions observed in perilymph of the samples taken at given times after the first withdrawal within the average time of an acute experiment (3 5 hours) directly relates to the decrease in the mechanical transmission of sounds and in the transducer function of the hair cells Since the dilution of potassium ions appears lower than that of sodium ions a passage of potassium ions from endolymph into perilymph, not great enough however to cancel the phenomenon (dilution of this cation in perilymph) has been hypothesized The consequence of the potassium ion leakage would be a decrease of the endocochlear potential and a further progressive deterioration of cochlear function

7 Dynamic relationships also have been discovered between chemical electrophysiologic and morphologic variables of cochlear function in congenitally deaf Dalmatian dogs Histologic control evidenced that the only pathologic change of the cochlea in these about two years old dogs is the complete loss of the organ of Corti in all turns Cochlear microphonic potential is absent for pure tones of any frequency and intensity The concentration of sodium and potassium ions in perilymph is closer to the concentration of the same cations in the diluted perilymph of the second and third samples from living cats with normal hearing than it is from cats shortly after death. This indicates that at least in our experiments deafness and death change the concentration of both sodium and potassium ions in opposite ways. deafness decreases death increases it

The fact that the concentration of potassium ions in the perilymph of living Dalmatian dogs is less than that of sodium ions may be related to the loss of the hair cells and supporting cells of the organ of Corti. This may be explained by the assumption that a partial provision of potassium ions to labyrinthine fluids is assured by these cells

The correlation studies support the concept that perilymph and it is assumed endolymph also function not only as nutrient fluid media and transmitters of the mechanical energy of the incoming sounds, but also and is believed primarily as a physicochemical and electrochemical environment necessary for the accomplishment of the transducer function of cochlear and perhaps vestibular neuroreceptors

Because of the existence of these dynamic relationships between ion chemistry of perilymph and the microphonic response of the cochlea it appears that one may predict cochlear microphonic function by measurement of the ion chemistry in perilymph and vice versa By doing this not only in laboratory animals but in humans as well during surgery the day is not too distant when hearing capacity of the cochlea will be evaluated from perilymph chemistry Conversely the electrochemical properties of perilymph and their modifications by drugs applied to the round or oval windows or administered systemically will be estimated from measurement of cochlear microphonics recorded at the round window

We believe that knowledge of the relationships between chemistry of the inner ear fluids and labyrinthine biopotentials will be of a great importance in understanding and investigating the physiology and pathophysiology of the inner ear

This knowledge also will facilitate the appropriate control of the disorders of cochlear and vestibular functions by use of drugs affecting the physicochemical properties of labyrinthine fluids directly or indirectly through the blood circulation and the metabolic changes elicited in tissues related to hearing and equilibrium

8 The present study of basic biochemical and physiological correlates of the cochlear function deserves attention also because of its clinical implications On the basis of the results of the experiments described in Item 5 and the estimation of the total volume of perilymph contained in the cochlea of cats and humans, the volume of perilymph loss in man that could produce the same disturbance of cochlear function discovered in the cat after the withdrawal of more than 4 16 cu mm perilymph has been calculated to be equal to 13 1 cu millimeters This is 17 per cent or 1/6 of the estimated total perilymph in human cochlea (78 3 cu mm) The proof that this is correct may be established by further experiments It must be proved also that the disturbance of cochlear function caused by removal of a given volume of perilymph at a given time is reversible in laboratory animals as well as in man. In the cats of this study the tendency of cochlear function to recover within one hour after the first sampling of perilymph appeared to fade gradually after the second hour of experimentation These observations suggest that the loss or leakage of perilymph during and after stapedectomy or any other ear surgery involving the perilymphatic space could be a factor potentially dangerous for cochlear function

Abstract

1 The results of the author s investigation of labyrinthine fluids and their role in cochlear physiology (a correlation study between ion chemistry of perilymph and microphonic function of the cochlea in the cat and Dalmatian dog) are reported Emphasis is given to the conclusion that labyrinthine fluids play a crucial role in the excitation process of cochlear and vestibular neuroreceptors The implication of the results in clinical otology i e. the possible disturbance of cochlear function following removal or leakage of a given volume of perilymph (volume which has been measured in the cat and estimated in man) during or after microsurgery of the ear is also discussed

2 Physical properties chemical composition and electrophysiologic aspects of the inner ear fluids are discussed in comparison with those of blood and cerebrospinal fluid and presented in table form in the Appendix to Chapter II.

3 Cochlear and vestibular physiology is critically reviewed at the light of the most recent data of the literature and new avenues of experimental and clinical research suggested.

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VENTILATORY STUDIES ON THE EUSTACHIAN TUBE

A Clinical Investigation of Cases with Perforated Ear Drums

BY

KNUT FLISBERG

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ACTA OTO-LARYNGOLOGICA
SUPPLEMENTUM 219

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Contents

Introduction and aim of the investigation

In recent years the Eustachian tube function has attracted increasing attention. The reason is that disturbances of this function have proved to give middle ear trouble on different occasions i. e during flying or diving when critical situations may arise if the Eustachian tube does not function properly

The author's attention has been drawn to the importance of a thorough knowledge of the Eustachian tube function for modern middle ear surgery Thanks to available antibiotics and a better technique there are now better possibilities to operate successfully for improvement of hearing in cases of chronic otitis media. A perfect and lasting operative result with a normal middle ear function depends, however on several factors. Among these the Eustachian tube function is an essential one. Pre-operative examination of the tubal function must be regarded as no less important than testing of the hearing function. The Eustachian tube function, however has not always been satisfactorily considered at the pre-operative assessment of the patient since the methods for studying this function have not been suitable. In spite of an excellent surgical technique, an operation may fail because of a poor Eustachian tube function.

On the whole the anatomical and histological structure of the Eustachian tube has been well known for a long time. The physiological and pathophysiological conditions however have been more difficult to evaluate and have for this reason been vividly discussed.

The functions that have been attributed to the Eustachian tube are *ventilation drainage* and *protection* of the middle ear By the ventilatory function is meant the capacity of the Eustachian tube to admit air passage into the middle ear to keep pressure equilibrium on both sides of the ear drum. Under normal conditions this ventilatory function of the Eustachian tube is probably the most important of the functions referred to

The Eustachian tube must be regarded as part of a functional unit that also consists of the middle ear the air cell system and the ear drum. An attempt to analyse all these factors simultaneously with regard to each other is a very complex enterprise. The author has restricted his examination only to an investigation of the ventilatory function of the Eustachian tube.

Earlier methods for pre-operative assessment of the ventilatory function were based on observations as to whether a pressure controlled or uncontrolled and applied in the rhinopharynx during swallowing, caused passage of air to the middle ear In such tests air is *forced* into the middle ear

From a physiological point of view however air is *sucked* into the middle ear when the Eustachian tube opens. The reason for this is that normally the pressure in the air space of the ear continuously falls slowly because of uptake

of gas from the middle ear From the point of view of normal physiology therefore it would appear more suitable to test the Eustachian tube by a method based on application of underpressure in the ear and to study the ability of the ear to equilibrate this underpressure. Such a method has been described by Flisberg, Ingelstedt and Örtegren (1963) (preliminarily read before the Swedish oto-rhinolaryngological Society in December 1961) and called the aspiration method.

Anatomically the Eustachian tube and the middle ear may be considered to be a part of the upper airway Since ventilation of the middle ear takes place through the Eustachian tube there are physiological similarities with the upper airway but also of course, great differences. Thus ventilation of the middle ear occurs only during the short moments when the Eustachian tube is opened, and then only for equilibration of pressure. As the Eustachian tube functions as an organ ventilating the middle ear it is obvious that its function may be discussed according to principles used in respiratory physiology During the opening period of the Eustachian tube the same principles as those used in the airways would then be applicable.

The aim of the present investigation, which was restricted to ears with perforated ear drums was

1 to work out refined methods for evaluation of the ventilatory function of the Eustachian tube.

2 to apply the new methods to normal ears, ears with chronic otitis media, and ears with patulous tubes.

3. to compare the new methods with some earlier methods for evaluation of the Eustachian tube function and judge their usefulness in clinical work with special reference to pre-operative assessment of tubal function.

Survev of symbols

Parts of the system of the Eustachian tube nose and ear

Et – Eustachian tube

M – Middle ear

N – Nose (including rhinopharynx)

Measured quantities

V – volume expressed in millilitre (ml) or microlitre (μl)

P – pressure relative to atmospheric pressure expressed in cm H_2O or mm Hg

P_N – pressure in nose

P_M – pressure in middle ear

P_F – pressure generated in middle ear system by a fan

Δp – change in pressure

$\dot{V}$ – air flow expressed in millilitre per second (at calibration procedures expressed in millilitre per minute)

Derived quantity

R – air flow resistance the ratio Δp (cm H_2O) to simultaneous $\dot{V}$ (ml/sec.)

In figures illustrating air flows the following symbols were used

a – starting of pressure application

b – opening of the Eustachian tube (at deglutition)

c – point of maximum air flow through the Eustachian tube

d – closure of the Eustachian tube

e – end of pressure application

f – beginning of level in air flow

Structure as a basis for the Eustachian tube function

This description only concerns data of importance for the present investigation [For detailed reviews see Zöllner (1942) Graves and Edwards (1944) Terracol (1949) Perlman (1951) Aschan (1955) and Berendes et al. (1965)]

The Et is a tubular S-shaped organ of 31–38 mm of length (Graves and Edwards 1944) connecting the middle ear with the rhinopharynx. It consists of an osseous part—the posteriolateral third which can be considered as an extension of the middle ear and a cartilagineous part which constitutes the anteriomedial two thirds. *The connection between the cartilagineous and osseous parts is* called the isthmus and constitutes the anatomically narrowest part of the Et towards which the tube narrows hourglass-wise.

CARTILAGE

According to the general description a cross section of the tubal cartilage forms a shepherd s crook with a medial bigger and a lateral smaller part. In the groove between these cartilagineous lamellae is located the real mucous membranous tube which is slightly movable. The medial wall of the Et consists of the big cartilage lamella. Laterally the small lateral cartilage is continued by a tendon disc which constitutes the main part of the lateral wall and by the fascia salpingopharyngeus The floor of the Et consists of a fascia running to the levator veli palatini muscle Between the walls of the mucous membranous tube and these fascias there is tissue consisting of fat cut through by streaks of connective tissue.

The cartilage is mainly of a hyaline structure but also contains elastic elements. The elastic component is considerably bigger in adults than in children (Aschan 1954) Zöllner (1942) and Aschan (1954) have also pointed out that the cartilage is richest in elastic tissue at the point where the medial and lateral cartilage parts are connected. The perichondrium and the submucosa have also a high proportion of elastic fibres (Guild 1955) in that part of the Et. This structure with a concentration of elastic fibres in and around the upper part of the tubal cartilage makes possible the spring effect which causes the closure of the Et. The closing mechanism probably operates quite passively firstly because of this spring effect of the cartilage and secondly because of the elasticity and pressure exerted by the surrounding tissues (Zöllner 1942 Guild 1955) According to Perlman (1939) the muscle tonus also plays a part in the closing mechanism.

MUSCLES

nions have been divided as to the normal condition of the Et. A summary he views on this question has been given by McMyn (1940)

Nowadays it is established that the Et is normally closed at rest and that e is no active muscular closing mechanism.

The tubal opening, however takes place above all at deglutition by muscle vity The muscles connected with this opening mechanism of the Et consist he tensor veli palatini muscle the levator veli palatini muscle and the sal opharyngeus muscle. The Et is opened mainly by contraction of the tensor palatini muscle. This muscle takes its origin from the base of the skull veen the spina angularis of the sphenoidal bone and the pterygoid process n the lateral lamella of the tubal cartilage and from the fascia salpingo- ryngeus Its tendon passes round the hamulus os pterygoideus where it is ly attached, and ends in the aponeurosis of the soft palate. The opening ction of this muscle was described for the first time by Valsalva (1704) ed from Macbeth, 1960) and verified by experiments on dogs by Politzer 61) and Rich (1920)

The opening is effected by pulling of that part of the tensor veli palatini scle which takes its origin from the lateral cartilage. The cartilage then olls a little and the lumen can be opened. Probably there is also a certain rect muscular influence on the mucosal tube from the connective tissue aks that cut through the tissues surrounding the tube (Zöllner 1942)

By direct stimulation of the tensor veli palatini muscle in dogs Holborow 62) proved that this muscle was responsible for the opening of the Et. The ning was made impossible by cutting the muscle.

The levator veli palatini muscle takes its origin from the inferior surface of petrous portion of the temporal bone anterior to the orifice of the carotid al. It passes under the Et parallelly with the tubal cartilage. The levator veli atini muscle ends in the soft palate where the muscles from both sides are nected with each other

The salpingopharyngeus muscle takes its origin from the medial and inferior ner of the tubal cartilage and branches out in the muscles that form the eral wall of the pharynx.

According to McMyn (1940) Zöllner (1942) McGibbon (1942) and Aschan 955) the levator veli palatini and possibly also the salpingopharyngeus muscle y have a synergistic effect with the tensor veli palatini muscle in the opening chanism of the Et when contracting. The levator veli palatini muscle would n assist in the opening process by elevating the medial cartilage.

INNERVATION

e motor innervation of the tensor veli palatini muscle has been studied and ucidated by Politzer (1861) and Rich (1920) They have shown on dogs that s muscle is innervated by the third branch of the nervus trigeminus via the

otic ganglion. There are different views on the motor innervation of the other muscles. Thus Graves and Edwards (1944) consider that the levator veli palatini muscle is supplied by the vagus nerve, whereas Rich (1920) is of the opinion that the vagus or the accessorius nerve is responsible for the innervation of this muscle.

The sensory nerve supply of the Et takes place either via the trigeminal nerve or the glossopharyngeal nerve. Thus Erickson (1935) found complete anesthesia of the Et following intracranial section of the glossopharyngeal nerve. Dandy (1927) and Stookey (1928) pointed out that the pharyngeal orifice of the Et forms a part of the area of supply of the glossopharyngeal nerve. According to Graves and Edwards (1944) the pharyngeal tubal orifice may also be innervated by the trigeminal nerve. This finding may be explained by the pharyngeal nerve supply from the sphenopalatine ganglion

According to Terracol (1949) the vegetative innervation of the Et proceeds from the trigeminal branches via the sphenopalatine and otic ganglions. By way of comparison it may be mentioned that the sphenopalatine ganglion also sends sympathetic and parasympathetic branches to the mucous membranes of the nose (Larsell and Fenton 1936)

MUCOUS MEMBRANE

The mucous membranes forming the real lumen of the Et consist of a ciliated columnar epithelium of the same type as that in the upper airway (Eggston and Wolff 1947) and a tunica propria This tunica propria is dividable into three layers basement membrane, lymphoid layer and glandular layer The mucous membrane is folded by rugae of the same type as in the gut (Moos 1874 Eggston and Wolff 1947) Citelli (1905) (cited from Graves and Edwards 1944) points out that because of intervening layers of lymphatic tissue the lymphoid layer is best developed in children and less so in adults Aschan (1954 1955) however found no lymphatic tissue in the tubal mucous membranes. According to Polvogt and Babb (1940) there is an elaborate lymphatic and vascular network in the lymphoid layer which is particularly pronounced in children. This may be partly responsible for the rough character of the mucous membrane

Because of the character of the mucous membrane with its mucous glands the inner surfaces of the Et easily stick together At the opening of the Et this occlusion must be broken. As early as 1869 Cleland pointed out that a film of moisture occludes the tube The surface tension may be of some importance in this mechanism so that the mucous membranes in the cartilagineous part of the Et are glued together (Flisberg, Ingelstedt and Örtegren 1963) The character of the secretion must play a certain rôle in the process. McMyn (1942) Aschan (1955) and Flisberg, Ingelstedt and Örtegren (1963) discuss the possibility that at the contact between the moist mucous membrane surfaces the capillary power must be of importance as a factor in the closure of the Et.

Normal ventilatory function of the Eustachian tube

From a ventilatory point of view the normal Et function is to keep a pressure equilibrium between the atmosphere and the middle ear However there may normally exist a slight underpressure in the middle ear depending above all on the uptake of gas from the middle ear This procedure is a complex one and depends in its turn on i. a. the state of the mucous membrane and its area. The pressure drop must of course also depend on the volume of air in the system.

The mucosa of the air cells is normally less vascular than the mucosa of the middle ear During operation on normal ear cases it is easy to observe that the mucous membrane lining the promontorium and the ear drum seems to be much more abundantly vascularized than the thin mucosa lining the accessory air space. In Rauber Kopsch (1955) it is also pointed out that the mucosa of the mastoid cells is poorer in blood vessels Therefore the main resorption of gas would take place from the middle ear mucosa. An underpressure because of gas resorption would therefore originate slower in ears with big than in ears with small air cell systems.

The equilibration of pressure taking place through the Et means that air is sucked into the ear i. e an aspiration of air takes place. This equilibration normally occurs mainly at swallowing. According to Graves and Edwards (1944) the frequency of deglutition in adults is once per minute when awake and once every fifth minute when asleep (in infants more frequently) The Et does not, however open at every deglutition (v Gyergyay 1932 Perlman 1951 Aschan 1955) The time during which the Et is open and equilibration can take place is very short. According to Perlman (1951) Aschan (1955) and Miller (1965) the time varies between 0.12 and 0.60 seconds.

It is a wellknown fact that the Et may function like a valve mechanism. Thus an underpressure in the middle ear or an overpressure in the atmosphere usually requires an active tubal opening for pressure equilibration. A high overpressure in the tympanic cavity on the other hand, may easily force the Et open (Hartmann 1879) Normally all equilibrations take place at deglutition without difficulty and without being noticed. During certain conditions however also a normally functioning Et can be thrown out of gear Such pressure changes can occur during flying when extreme pressure variations may take place very rapidly If in such circumstances the overpressure in the atmosphere becomes too high a locking of the Et can take place It is then impossible for the muscles of the tube to open it since the fibro-cartilagineous part of the Et that is elastic and yields readily to pressure (Bryant 1907) collapses completely Zöllner (1942) has pointed out that the fossa Rosenmülleri is of importance in this mechanism. According to Armstrong and Heim (1937) such locking of the

Et—from the outside—occurs at a relative overpressure in the atmosphere exceeding +90 mm Hg The phenomenon which is a man-made problem has been illustrated by McGibbon (1942) with the aid of an ear Et model and called pressure occlusion

Ventilatory function during pathological conditions

The tissue factors causing passive closure of the Et counterbalance the muscular opening mechanism. The concept tissue factors covers the elasticity of the cartilage, the properties of the mucous membrane, and the pressure and elasticity of the tissues surrounding the Et.

A disturbance in the balance between opening and closure mechanisms gives a disturbed function in the Et.

A normal muscle activity is of vital importance for the opening of the Et and the ventilation of the middle ear This is best shown in cases where the muscles of the palate and the Et do not function normally i. e. in children with cleft palates. In these cases hearing impairment of a conductive nature is often found in more than 50 % (Holmes and Reed 1955 Drettner 1960 Holborow 1962) This hearing impairment is caused by malfunction of the muscles of the Et (Gaines 1940 Holborow 1962) which cannot effectively open the Et for ventilation of the middle ear

Hearing impairment has also been demonstrated after occlusion of the Et by placing a small inflatable rubber balloon in the nasopharynx (Lock 1942 Herberts 1948)

By pneumophone measuring in the ear canal van Dishoeck (1941) found underpressures in the middle ear down to –60 cm H_2O He concluded that the reason for the underpressure was a high resistance of the Et.

A change of the conditions of the tissue factors may give function disturbances which in principle may be of two kinds either the tube cannot open or it is continually open.

It is wellknown that in the middle ear adherences and thickening of the mucous membranes can occur after infections. This may also probably take place in the Et. As a result of these changes stenosis of the tubal lumen can appear In cases of longstanding infection it is also possible that more far reaching changes in cartilage and tissues may occur Difficulties at tubal opening and equilibration of originated underpressures in the middle ear may be the consequence. There is then a certain danger of chronic lesions to the middle ear Of these lesions chronic otitis media is the most serious.

It seems generally accepted that inflammatory middle ear diseases occur more commonly in ears with a poorly pneumatised air cell system (Diamant 1940) The connection between the Et function and the pneumatisation of the bone of the ear is however not clear Ojala (1957) has shown that the pneumatisation of chicken humerus can be checked by permanent occlusion of the foramen pneumaticum together with a slight inflammatory process in the air space of

the bone. It is not clear whether the circumstances are the same after occlusion of the Et in man.

If the tubal opening is impossible however the result is a negative pressure in the middle ear

Bezold (1883) was of the opinion that a non inflammatory transudation takes place in the middle ear after tubal blockage the so-called ex vacuo theory Opinions contrary to the ex vacuo theory have been put forward by e.g Zöllner (1942) and Senturia et al (1962) who are of the opinion that serous otitis must be looked upon as an inflammatory or allergic middle ear disease and is very seldom produced by vacuum.

The occlusion of the Et can be compared with a blockage of a bronchus of the lung In the lung this means atelectasis of the lung, a lobe or a part of a lobe—in the ear atelectasis of the whole middle ear and air cell system.

Flisberg, Ingelstedt and Örtegren (1963) and Flisberg (1964) showed that at falling negative pressure in the middle ear the normal ability to aspire is first more and more impaired while inflation still takes place easily (This was in fact suggested by E. P Fowler (1920) who observed vacua in the middle ear varying between 10–15 mm Hg, though in tubes which opened even at gentle inflation.) This form of tubal "locking could be seen in normal subjects at high negative pressures in the middle ear but at very moderate middle ear negative pressures during common cold

Flisberg, Ingelstedt and Örtegren (1963) further observed negative pressure spikes in the ear produced by swallowing especially in cases of common cold during the locking period This phenomenon (called the negative dip phenomenon) must be produced by an increase of the ear space volume. Such an increase can be due to a separation close to the isthmus of the mucous membranes that are glued together

It seems quite clear that the condition of the mucous membrane must be of great importance for the air passage through the tube Thus oedema of the membrane as well as vascular factors should be essential. The importance of the vascular factor for the function is clear from the fact that a continually open Et—patulous tube—generally closes after the patient is placed horisontally (Perlman 1939 Moore and Miller 1951) In this situation the hydrostatic pressure in the mucosal vessels is raised and the membranes swell so that the Et closes. During inflammatory conditions the lumen is also closed because of increased secretion, vascular congestion and oedema.

The cause of the patulous tube state is considered to be both a tissue factor and a muscle factor Owing to loss of tissue around the tube in connection with marked loss of weight in cases of debilitating disease (Moore and Miller 1951) patulous tubes can appear (Ostmann s theory of fat atrophy of the tube 1893) Handl (1959) pointed out that after retrogasserian neurectomy atrophy of the mucous membrane of the same side of the nose may be combined with a patulous tube This would then be due to trophic disturbances of the mucous membrane of the Et.

According to Perlman (1939) many cases of patulous tube are seen among

patients operated on by retrogasserian neurectomy because of trigeminal neuralgia. Perlman believes that a lack of tonus of the muscles that affect the Et (tensor veli palatini muscle) and are supplied by the fifth nerve is the principal factor in producing the clinical entity

Earlier methods for evaluation of the ventilatory function of the Eustachian tube

A detailed review of methods giving and indicating tubal passage has been given by Ingelstedt and Örtegren (1963)

The present investigation covers ears with a permanent ear drum perforation or ears where a perforation was produced by drum incision. This account will be restricted to methods that can be used when there is perforation of the drum.

The methods based on application of contrast media for X-ray studies (Rees Jones 1941 Welin 1947 Aschan 1954 Compere 1958) or application of tracer solution to the middle ear (Rogers Kirchner and Proud 1962) must be regarded as unphysiological from the ventilatory point of view These methods supply information on the pathological conditions of the Et and elucidate the ability of the Et to drain the middle ear They do not reflect the normal air ventilation.

METHODS GIVING TUBAL PASSAGE

UNCONTROLLED PRESSURE CHANGES IN THE RHINOPHARYNX

a) *Politzer s method*

In the middle of the 19th century Politzer introduced a method of testing the passage through the Et by forcing air from the nose into the ear For this purpose a bag was used which could be placed airtightly to one nostril and then compressed so as to raise the pressure in the rhinopharynx at swallowing. Another possibility was to force air into the middle ear through a tubal catheter introduced into the tubal pharyngeal orifice.

b) *Toynbee s manoeuvre*

Toynbee pointed out (1853) that a dump feeling depending on a pressure change in the ear appears at swallowing with the nose closed. The feeling does not disappear before the next act of swallowing. This method for bringing about pressure changes in the middle ear has been used as a function test of the Et by Zöllner (1942) and Thomsen (1958)

CONTROLLED PRESSURE CHANGES IN THE RHINOPHARYNX

Hartmann (1879) produced a controlled overpressure in the rhinopharynx by blowing a continuous air flow through the nasal cavity An estimate of the pressure at which the Et opened was then given This principle has later been

used by Zöllner (1942) Perlman (1943) Thomsen (1955) Oltersdorf (1962)

Ingelstedt and Örtegren (1963) worked out a pressure device for producing a constant square pressure wave in the rhinopharynx. The pressure at which tubal passage appeared was then determined.

METHODS INDICATING TUBAL PASSAGE

Indication of tubal passage during middle ear ventilation in cases with a per foration of the drum must be made either with recording of sound or with recording of pressure variation in the ear canal.

a) The simplest form of sound recording is auscultation in the ear canal, at which the sound changes produced at air passages through the Et or at application of sound in the nose can be heard by the investigator (Toynbee 1853 Lucae 1867 von Gyergyay 1932 Zöllner 1942) Perlman (1943) used this principle but completed it by threshold pressure produced in the nose

b) Objective recording of a sound conducted into the nose and transmitted to the ear canal at the tubal opening was made by Perlman (1951)

c) For recording of pressure changes in the ear canal Politzer (1861 1862) used an ear canal manometer (a droplet moving in a pipet) The same method has been used by Woyatcheck (1908) and Terkildsen (1956) A Marey capsula was used by von Gyergyay (1932) and Oltersdorf (1954)

d) For indicating tubal passage Juganov (1960) Oltersdorf (1962) and Ingel stedt and Örtegren (1963) used pressure transducers connected to the ear canal.

e) Ingelstedt and Örtegren (1963) described a flow rate meter device for in dicating tubal passage.

f) By determination of pressure changes in a rigid closed tank of known volume connected to the external ear canal Ingelstedt and Örtegren (1963) measured the volumes of air that passed the Et. They performed the in vestigation with their ear-snorkel-pressure chamber technique and could determine the air volumes passing through the Et in both directions.

PRESSURE VARIATION IN THE NOSE

As regards controlled pressures in the rhinopharynx during swallowing it is possible to quantitate the pressure necessary for obtaining tubal passage. Such investigations have earlier been reported only after testing ears with intact ear drums The results of these investigations are referred to in a comparison with the results of the present study

Hartmann (1879) found that an overpressure of 2–6 mm Hg (3–8 cm H_2O) in the nose gave passage through the normal Et during deglutition.

Zöllner (1942) made an investigation of the resistance of a normal Et in 200 airmen and got passage at 5 cm H_2O overpressure in the rhinopharynx in 68 % at 10 cm H_2O in 75 % and at 15 cm H_2O in 82 % of the cases (Zöllner determined tubal passage optically by an ear drum microscope)

Perlman (1943) made similar tests and got passage between 0–6 mm Hg (0–8 cm H_2O) overpressure in the nose in 10 cases of unobstructed tubes by inflation through the nose. In 3 cases with tubal obstruction the required pressures were 30–50 mm Hg (40–68 cm H_2O)

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(1958) found that 72 % had positive
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IN THE MIDDLE EAR

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P fter incision of the ear drum The pos

sibility of the ear to equilibrate this pressure was estimated, first when the tendon to the tensor veli palatini muscle was intact, and second, after it had been cut. When the muscle was made to contract the Et opened and the pressure applied in the middle ear could be equilibrated. This was impossible after cutting the tendon to the tensor veli palatini muscle.

Miller (1965) published a material of ears investigated by the same aspiration method as the present author (Flisberg, Ingelstedt and Örtegren 1963). Miller found that after incision of the drum normal ears could equilibrate an applied underpressure in the ear in 100 % whereas only 43 % of ears with chronic otitis media in his whole material could do this. As a measure of the resistance of the Et Miller used the residual pressure remaining after equilibration of negative pressure applied in the ear.

Van Dishoeck (1947) took the middle ear pressure as a measure of tubal resistance. He measured the intratympanic pressure by the pneumophon method (van Dishoeck 1937). On 400 healthy ears van Dishoeck found a middle ear pressure less than 10 cm H_2O in 93 % of the cases.

By measuring the impedance of the ear drum Thomsen (1957) determined the threshold pressure necessary in the rhinopharynx to get tubal passage. He found that 83 % of the persons (100 normal cases) had threshold pressures of 10 cm water or less. Thomsen also determined the capacity of the tube to reduce the overpressure produced in the middle ear by deglutition. In 73 % the cases could completely equilibrate the overpressure.

Earlier results

PRESSURE VARIATION IN THE NOSE

As regards controlled pressures in the rhinopharynx during swallowing it is possible to quantitate the pressure necessary for obtaining tubal passage. Such investigations have earlier been reported only after testing ears with intact ear drums The results of these investigations are referred to in a comparison with the results of the present study

Hartmann (1879) found that an overpressure of 2–6 mm Hg (3–8 cm H_2O) in the nose gave passage through the normal Et during deglutition.

Zöllner (1942) made an investigation of the resistance of a normal Et in 200 airmen and got passage at 5 cm H_2O overpressure in the rhinopharynx in 68 % at 10 cm H_2O in 75 % and at 15 cm H_2O in 82 % of the cases (Zöllner determined tubal passage optically by an ear drum microscope)

Perlman (1943) made similar tests and got passage between 0–6 mm Hg (0–8 cm H_2O) overpressure in the nose in 10 cases of unobstructed tubes by inflation through the nose. In 3 cases with tubal obstruction the required pressures were 30–50 mm Hg (40–68 cm H_2O)

Using Zöllner's method for application of pressure in the nose and recording tubal passage by determination of changes of the ear drum impedance, Thomsen (1957) got passage in 83 % of the normal cases up to 10 cm H_2O overpressure in the nose.

Using Toynbee's manoeuvre which does not give a clearly defined pressure change in the rhinopharynx Zöllner described an investigation of 200 ears (1942) in which he got positive passage in 70.5 % of the cases.

In a series of normal ears Thomsen (1958) found that 72 % had positive Toynbee's manoeuvre, i e. showed passage through the tube.

PRESSURE VARIATION IN THE MIDDLE EAR

For evaluation of the Et function studies based on pressure changes in the middle ear are far more interesting from a physiological point of view

Von Gyergyay (1932) made experiments on perforated ear drum cases with Toynbee's manoeuvre and got an underpressure in the middle ear He also observed but did not discuss the fact that the patient equilibrated the under pressure by swallowing

Holborow (1962) made experiments on anesthetized dogs to show the effect of the tensor veli palatini muscle on the mechanism of the tubal opening. Pressure was applied in the middle ear after incision of the ear drum. The pos-

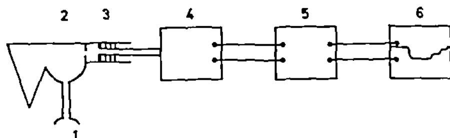


Fig. 1 Block diagram of equipment used in pressure measurements in the ear 1. Et and epipharynx 2. Air filled ear space 3. Rubber cuff 4. Pressure transducer 5. Amplifier 6 Recorder

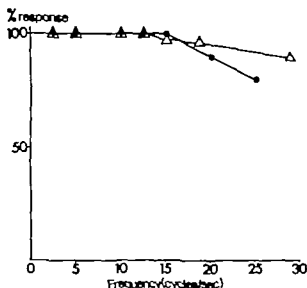


Fig. 2 Frequency response curves for pressure measurements in ear and nose.

△—△ Manometer system for recording pressure variation in the ear
●—● Manometer system for recording pressure variation in the nose.

FLOW MEASUREMENTS

For the investigation a flow rate meter device consisting of a differential pressure transducer with resistors, amplifier and recording unit was used. Block diagram of the equipment is given in fig. 3.

The differential pressure transducer had a working pressure range of ± 50 mm water level (pneumomanometer EMT 572 Elema Schönander AB Stockholm)

Different resistors could be connected to the differential pressure transducer by identical catheters which had the same damping effect. This was measured by giving sine pressure waves to both catheters simultaneously The membrane

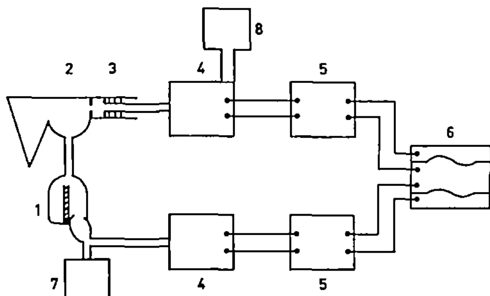


Fig. 3. Block diagram of equipment used in combined pressure and air flow measurements. 1 Et, epipharynx and nose; 2 Air-filled ear space; 3. Rubber cuff, 4. Pressure transducer 5. Amplifier 6 Recorder 7 Equipment for giving square pressure waves in the nose 8 Equipment for giving under and overpressures in the ear

of the differential pressure transducer should then not move and cause any electrical signals.

As resistors in the flow meter device could be used a Fleisch pneumotachograph nr 2040 as well as glass capillaries of different calibres and lengths coupled parallelly between two collecting units of glass.

Three different resistor systems with 5 glass capillaries in each were devised. The different resistors were called

I. (length of capillaries 120 mm inner diameter 0.8 mm)
II. (length of capillaries 140 mm inner diameter 1 0 mm)
III (length of capillaries 50 mm, inner diameter 1 5 mm)
IV (pneumotachograph nr 2040)

The pressure variations were amplified and recorded on a Visicorder (model 906 S Honeywell)

Calibration procedure

The flow meter device was calibrated with known constant air flows. Constant air flows were produced from gas tight glass syringes driven by an infusion device with a synchronous motor and different switches and by a rotameter (predictability flow meter FN 1044 B) In the case of the glass syringes absolute calibration was performed by filling the syringes with water and producing

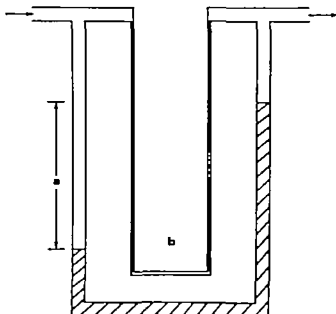


Fig. 4. Sketch of water differential manometer with resistor used at calibration procedures.
a. Distance between water levels during constant air flow through the manometer device·
b Exchangeable resistor

different flows between 2.4 and 75 ml/min. by using different speeds on the infusion device. The water volumes obtained after a fixed time could then be determined. For air flows from 75 ml/min. up to 850 ml/min. the rotameter was used. Absolute calibration of the air flows from the rotameter was made by water displacement.

The known constant air flows passed through a differential water manometer (see fig. 4) It was possible to vary the sensitivity of the water manometer by using three different resistors. An example of a calibration curve for this manometer is given in fig 5.

As a matter of routine the water differential manometer was used as a basis for the absolute calibration of the flow meter device. The calibration was carried out for every investigation with the catheter system connected to the flow meter device This was effected by placing the cuff airtightly in an artificial ear canal.

Resistor I was calibrated with known air flows and used up to an air flow of 55 ml/min. Resistor II was used up to 150 ml/min., resistor III up to 450 ml/min. and resistor IV i. e. the pneumotachograph, calibrated for use up to 850 ml/min. An example of calibration curve for the flow meter device equipped with resistor II has been given in fig 6

Frequency response analysis of the entire recording system (catheter and flow meter device equipped with the different resistors) was performed. This was made on model experiments where cuff and catheter were lodged in an

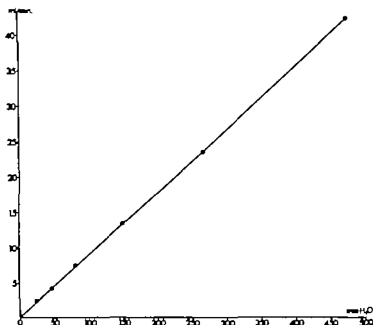


Fig. 5. Calibration curve for the water differential manometer in fig. 4 with constant known air flows. Resistor giving highest resistance was used.

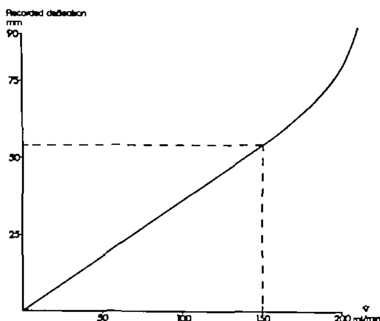


Fig. 6. Calibration curve for the flow meter device equipped with resistor II (see text) With this resistor the flow meter device was used up to 150 ml/min, which means a recorded maximal deflection of 55 mm on the scale of the recorder

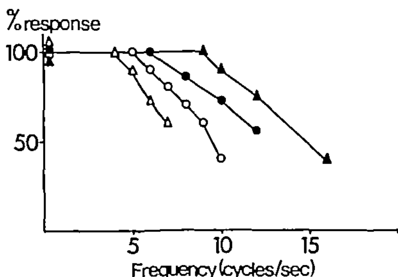


Fig. 7 Frequency response curves for the flow meter device equipped with the different resistors.

Resistor I △—△ Resistor III ●—●
II ○—○ IV ▲—▲

artificial ear canal. The given air flows were shaped as sine waves. The frequency response was calculated from the integrated curve The frequency response curves are given in fig 7 The recording system must be sensitive enough. For this reason the system used was compared with another system where the frequency response was adequate up to 15 cycles/sec. This was performed on model as well as on patient experiments. The investigations showed that the different resistors provided adequate reproduction of all air flow rates obtained.

The frequency analysis was completed by an investigation with volumes added to the system in an effort to mimic the damping effect of different air cell systems With added volumes of 5 and 10 ml no difference was given in the frequency representation.

The sensitivity of the flow meter device was so adjusted that maximum recording on the amplifier gave a recorded deflection of 65 mm on the scale of the Visicorder

Integrator unit

The air flow could be integrated, whereby the total air volume passing through the Et was determined.

For the integrating circuit absolute calibration was made by determining the slope of the recorded integrated signals during known constant air flows.

Known air volumes produced by gas tight syringes (volumes 50 250 1000, 5000 microliters) were further made to pass through the flow meter device. Calibration of this kind was performed in connection with every investigation.

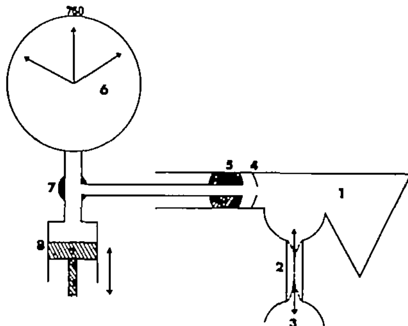


Fig 8 Ear manometry Aspiration or deflation methods 1 Air-filled ear space; 2 Et; 3. Epipharynx· 4. Ear drum, 5. Rubber cuff 6. Manometer· 7 3-way stopcock 8 Syringe (for producing desired pressures in the system)

EXAMINATION PROCEDURES

EVALUATION OF THE EUSTACHIAN TUBE FUNCTION BY PRESSURE MEASURING IN THE EAR (EAR MANOMETRY")

The method implies that pressure changes induced by deglutition in the closed ear manometer system is taken as an expression of the ventilatory ability of the Et. A pre-requisite for using the method was free air passage between the ear canal and the middle ear i. e. a perforation in the ear drum should already exist or such a perforation had to be made by incision

If a closed manometer system was airtightly connected to the external ear canal (fig 8) an applied under or overpressure in the system would remain unchanged for a short length of time till the Et opened, for example by swal lowing. Pressure variation in the closed ear-manometer system could be produced by the investigator The degree of pressure change as well as changes occurring as a result of air passage through the Et were recorded.

EVALUATION OF AIR FLOW DIRECTION

At the *opening of the Et air passes through the tube if there exists a pressure* difference between the two ends of the Et. The direction of the air flow is con trolled by the pressures in the middle ear and the epipharynx.

For measuring of air flow direction the same equipment as that for pressure

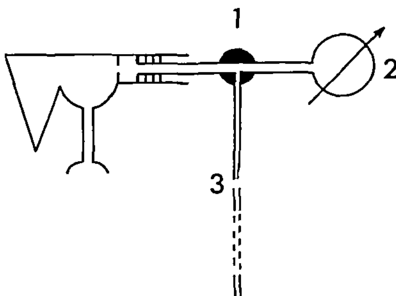


Fig. 9. Principle of measuring air flow direction by using open ear manometry 3-way stop-cock Manometer 3. Catheter of variable length.

measurement in the ear was used, but the system could also be kept open (open ear manometry") according to fig. 9. The length of the catheter used during measurement with open system was variable.

The pressure difference across the Et at measuring with closed system was performed by applying pressure in the middle ear and by swallowing with the nose closed (Toynbee s manoeuvre) By investigations with open system the pressure difference was performed only by Toynbee s manoeuvre.

EVALUATION OF THE EUSTACHIAN TUBE FUNCTION BY COMBINED PRESSURE AND AIR FLOW MEASUREMENTS

The purpose was to study the resistance to air flow offered by the Et during different conditions by using the methods and principles currently employed in respiratory physiology

The air flow (V) through and the pressure differene (Δp) over the part of the airway that will be estimated are determined. The air flow resistance (R) is then $= \frac{\Delta p}{V}$ (DuBois 1962, Comroe 1964)

It is possible to measure the pressure difference over and the air flow through the Et simultaneously and in this way to calculate the resistance according to the formula given above (Flisberg 1966)

The middle ear was connected airtightly to the described flow meter device

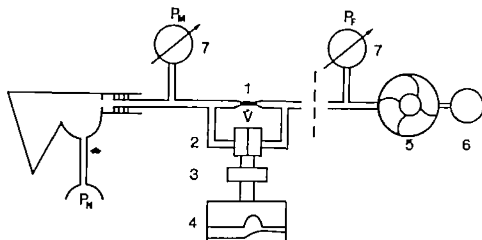


Fig. 10. Principle of air flow measurements. 1 Resistor in the flow meter device 2. Differential pressure transducer· 3. Amplifier· 4. Recorder· 5. Electric fan 6. Autotransformer· 7 Manometer P_F = pressure generated by an electric fan P_M = pressure in the middle ear· P_N = pressure in the nose.

by means of a nylon catheter (inner diameter 2 mm) running through an inflatable cuff placed in the bony part of the external ear canal. The other side of the flow meter was open to the atmosphere or could be connected to an electric fan (fig 10) By the fan desired pressures could be applied in the ear (Different pressures in the nose were given as square pressure waves—see p 31) When an air flow passed through the Et in one direction or the other it also passed through the flow meter device and caused a pressure difference over its resistor This pressure difference was measured and recorded.

The errors arising from recording and calculating the air flows were analyzed (see statistical note) With few exceptions the error was less than ±20 %

The errors in calculating the pressure differences were always less than ±5 %

Depending on the construction of the integrating circuit there was an error in the integrated curve which varied with the time constant. By always using 20 sec. as time constant the error was less than 1 5 % during investigations where the measuring did not exceed 0.5 sec. At 1 sec. the error had increased to 2.5 %

The pressure difference (Δp) over the Et could be determined by simultaneous measuring of the pressure in the ear and in the nose.

According to fig 10 $\Delta p = P_N - P_M$ during application of overpressure in the nose At testing with application of underpressures in the nose $\Delta p = P_M - P_N$.

At investigation with application of under or overpressures in the ear-manometer system $\Delta p = P_F - P_M - P_N$ In general the pressure change of P_M at air passage through the tube was here so small that it could be neglected in relation to P_F As the nose was open P_N was the same as the pressure in the atmosphere and could be stated as zero Thus in these testings $\Delta p = P_F$

The difference between P_F and P_M at air passage through the Et was the same as the measured pressure difference of the differential pressure manometer Because of the magnitude of P_F and P_M compared to the pressure change of P_M at air passage through the Et it was convenient to measure this difference by a differential pressure manometer

The ideal pressure measuring in the middle ear should have been performed in the middle ear as closely as possible to the aural part of the Et. To be able to carry out different investigations during identical circumstances the rubber cuff equipment was used and the pressure was measured outside the ear The pressure drop which must then appear over the cuff with the catheter was determined in model experiments. The rubber cuff with the catheter was applied in an artificial ear canal and different air flows were made to pass through it. The pressure drop over the catheter at an air flow of 14 ml/sec. was 13 6 mm H_2O at an air flow of 6 5 ml/sec. 6 mm H_2O and at air flows up to 2.5 ml/sec. less than 2 mm H_2O

At air flows through the resistor in the flow meter device a certain amount of counterpressure must arise This counterpressure was determined for the calibrated maximal air flows used on each resistor For resistor I the counterpressure was 4 7 mm H_2O for resistor II 4 0 mm H_2O for resistor III 2.0 mm H_2O and for resistor IV 1 5 mm H_2O

The total counterpressure was small and did not exceed 15 mm H_2O for air flows less than 14 ml/sec. At general recorded air flows the counterpressure seldom exceeded 6 mm H_2O

Calculation procedures at air flow measurements

Pressure changes, air flows and integrated air flow signals were recorded simultaneously on the Visicorder

The air flow at a certain point was determined by measuring the height of the deflection of the air flow curve at this point. This value was then entered on the calibration curve for the resistor used.

At determination of the air volume passing through the Et the height of the integrated curve was measured. The height was an expression of the air volume that had passed up to the measuring time point. Every recorded mm then meant a fixed volume which was different for every resistor in the flow meter device. Thus every mm recorded deflection on the integrated curve indicated for resistor I 7 microliters for resistor II 17 microliters for resistor III 100 microliters for resistor IV 167 microliters.

The air flow resistance offered by the Et was expressed in cm H_2O per ml/sec.

STATISTICAL NOTE

(in collaboration with F K. Mats Lörstad, Department of Statistics, University of Lund)

The magnitude of the error of measurement was estimated by taking into account the linear dependence between the three variables x, y and z, where x is the calibrated constant

air flow y the distance between water levels on the differential water manometer and x the recorded deflection. It was only possible to make observations of the pairs (x y) and (y z) of the variables, where the value of the first variable in the pairs was chosen in advance. The regression line was computed for the two pairs by means of the method of least squares and thus the two residual variances were estimated from the formulas:

$$s^2_{y} = \frac{(n-1)\ s^2_{y}}{n-2}\left(1-r^2_{yx}\right) \text{ and } s^2_{z\cdot y} = \frac{(n-1)\ s^2}{n-2}\left(1-r^2_{zy}\right)$$

Finally an estimate of the residual variance of z in its dependence of both y and x was arrived at by means of the formula

$$s^2_{z(y,x)} = b^2_{z\cdot y}\ s^2_{y\cdot} + s^2_{z\cdot y}$$

(This formula is derived from statistical textbooks i.e. Rao C. Radhakrishna Linear Statistical Inference and Its Applications. Chapt. 4. New York 1965.)

The assumptions necessary for making this formula valid are independence between the errors of x, y and z, and independence between the error and the value of the variable. The errors must be normally distributed.

To relate the errors of measurement in z to a simple form 3σ-limits were computed and divided with a value in the middle of the range for each resistor in the flow meter device.

The 3σ-error in per cent for each resistor at mid value of z then was I. ± 14 % II. ± 9 % III ± 17 % IV ± 12 %

Other Eustachian tube function methods used

POLITZER S METHOD

By increasing the pressure in the nose with a Politzer s bag while the patient swallows it is possible to force air into the middle ear In fig. 11 the lower curve of the Politzer procedure illustrates the pressure variation in the nose and the upper curve the pressure variation in the ear

CRADED INFLATION

A pressure was applied in the rhinopharynx as a square pressure wave simul taneously with the patient s swallowing Air passage through the Et was recorded with the same system as that used at pressure measurement in the

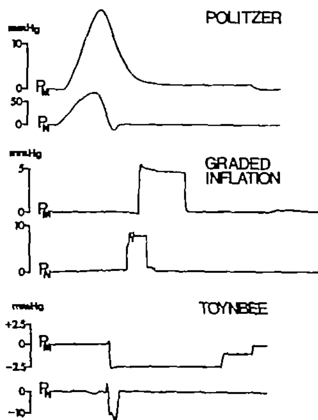


Fig Examples of pressure measuring in nose and ear at positive testings with Politzer s method, graded inflation and Toynbee manoeuvre.

ear The lowest pressure necessary for tubal passage was determined and a quantitative value of the ability to get tubal passage was given In fig 11 at the *investigation of graded inflation the pressure in the nose was changed by a* square pressure wave (lower curve) while the upper curve shows how the pressure changed in the middle ear

TOYNBEE S MANOEUVRE

By swallowing with the nose closed the pressure in the rhinopharynx is changed. The tube opens during the act of swallowing and a pressure variation in the ear is induced. An example of pressure changes in the nose and ear is seen in fig 11

Experimental procedures

Identical experimental conditions were preserved in the different investigations. The subject sat in an examination chair with a headrest. In some cases with patulous tubes the examination was also undertaken with the patient in a recumbent position. Swallowing was induced by letting the subject drink water The investigations were made as short as possible to minimize thermal influence.

Between the different testing moments there were pauses of 1/2–1 min. The underpressures were only applied during very short periods of time except during loading tests.

The following investigations were made

EAR MANOMETRY

Air passage through the Et was induced by the following methods

Politzer s method.

Application of graded positive pressures in the rhinopharynx (graded inflation) The pressures were +5, +10 +15, +20 +25, +30 and in some cases +40 cm H_2O

Toynbee s manoeuvre

Application of negative pressures in the middle ear (aspiration method) and testing of the capacity for equilibrating the pressure at swallowing The pressures were −2 −5, −10 −20 and −30 mm Hg.

Application of positive pressures in the middle ear (deflation method) and testing of the capacity for equilibrating the pressure at swallowing The pressures were +2 +5, +10 +20 and +30 mm Hg.

By *studying the negative dip phenomenon* close as well as open ear manometry was performed. Ordinary deglutition and Toynbee s manoeuvre were used to induce the phenomenon.

EVALUATION OF AIR FLOW DIRECTION

Toynbee's manoeuvre was used to produce pressure differences across the Et. During measuring with a closed system Toynbee's manoeuvre was combined with pressure application in the middle ear

EVALUATION OF THE EUSTACHIAN TUBE FUNCTION BY COMBINED PRESSURE AND AIR FLOW MEASUREMENTS

Air passage through the Et was induced by the following methods

Politzer's method.

Application of graded positive pressures in the rhinopharynx (graded inflation) The pressures were kept so that the pressure differences across the Et were +10 +20 +30 and in some cases +40 cm H_2O

Application of graded negative pressures in the rhinopharynx. The pressure differences across the Et were −10 −20 −30 and in some cases −40 cm H_2O

Application of negative pressures in the middle ear (aspiration method) and testing of the capacity for equilibrating the pressure at swallowing. The pressures were −10 −20 −30 and in some cases −40 cm H_2O

Application of positive pressures in the middle ear (deflation method) and testing of the capacity for equilibrating the pressure at swallowing. The pressures were +10 +20 +30 and in some cases +40 cm H_2O

The pressures in the ear during testing with the aspiration and deflation methods in air flow measurements were obtained by connecting a fan with that part of the flow meter device that faced the atmosphere.

Application of a constant underpressure in the middle ear

An underpressure of −30 cm H_2O was continually applied in the middle ear by a fan connected with the flow meter device as described above. The pressure was continually kept up to 25 minutes At intervals of 5 minutes the air flow through the Et during swallowing was recorded.

Material

Pressure measuring in the ear was performed on 102 patients with the diagnosis of chronic otitis media. All had central perforation of the ear drum and myringoplastic operations were considered. The investigation was performed at least twice on every patient on different occasions (intervals more than two weeks) (Tables I and II) In this material 6 ears with patulous tubes were found) (Table VII)

Attempts were made to divide the material according to the duration of the disease. There were great difficulties in obtaining reliable information about how long the patients had had perforations of their ear drums. The number of patients who could yield reliable information was so small that no conclusions could be drawn. Knowledge about the duration of the periods of discharge should also have been valuable. However it was found that also in this respect the patient s information was so unreliable that a valid estimation of the duration was not even attempted.

Pressure measuring in the ear was also performed on a material of 36 patients with healthy ears (Tables III and IV) In these ears incision of the ear drum had to be made before the testing In these cases the investigations could for natural reasons be performed only once. The investigation was made on healthy volunteers and in patients with tinnitus or hearing impairment of unknown origin. The length of the incision was at least 2–3 mm and the perforation was made in such a way that it remained open

There must be no history of otitis media or serous otitis. The drum should be normal and freely movable. In all these cases the perforation after incision healed up without complications.

Tables I and II. *Cases of chronic otitis media investigated by pressure measuring in the ear*
(Six cases of patulous tube are given in Table VII.)

Age distribution

Years	Number of ears
7–20	22
40	32
> 40	42
Total number	96

Sex distribution

Men	Women	Total number of ears
51	45	96

Tables III and IV *Cases of healthy ears investigated by pressure measuring in the ear*

Age distribution

Years	Number of ears
18–20	4
21–40	16
> 40	16
Total number	36

Sex distribution

Men	Women	Total number of ears
20	16	36

Tables V and VI. *Cases of chronic otitis media investigated by combined pressure and air flow measurements*

Age distribution

Years	Number of ears
12–20	8
21–40	20
> 40	13
Total number	41

Sex distribution

Men	Women	Total number of ears
21	20	41

Table VII. *Patulous tube cases*
Pressure measuring in the ear

Number of ears	Age in years	Men	Women
6	11 3 20 25, 33 39	1	5

Table VIII. *Patulous tube cases*

Combined pressure and air flow measurements

	Number of ears	Age in years	Men	Women
Cases with chronic otitis media	2	27 43	2	–
Cases with incision of the drum	5	7 22 44, 44, 56	3	2
Total	7	17–56	5	2

Combined pressure and air flow measurements were made on a series of 41 patients with chronic otitis media and central perforations of the ear drums (Tables V and VI)

Five patients with intact ear drums hade discomfort from patulous tube. In these cases incision of the ear drum was performed and investigation by com bined air flow and pressure measurements were made The perforations of the ear drums were about 3–4 mm long As in the case of the healthy subjects, they were made so as to remain open. The reason was that the air flow resistance must not increase. All incised ear drums healed up without complica tions (Table VIII)

In ears with chronic otitis media the perforations of the ear drum were so large that increased air flow resistance could be disregarded.

Investigations were made on suitable ears of the present material by measuring the air flow direction and by studying the negative dip phenomenon.

All ears with chronic otitis media had been dry and without discharge for at least one month before every examination. The patients had no complaints from the respiratory tract and no nasal obstruction or discharge from the nose. In addition to ear examination inspection of nose epipharynx and larynx were made in all cases. This examination did not reveal anything abnormal.

Tables III and IV *Cases of healthy ears investigated by pressure measuring in the ear*

Age distribution

Years	Number of ears
18–20	4
21–40	16
> 40	16
Total number	36

Sex distribution

Men	Women	Total number of ears
20	16	36

Tables V and VI. *Cases of chronic otitis media investigated by combined pressure and air flow measurements*

Age distribution

Years	Number of ears
12–20	8
1–40	20
> 40	3
Total number	41

Sex distribution

Men	Women	Total number of ears
1	20	41

Table VII. *Patulous tube cases*
Pressure measuring in the ear

Number of ears	Age in years	Men	Women
6	1 3, 20 25, 33, 39		5

Table VIII. *Patulous tube cases*

Combined pressure and air flow measurements

	Number of ears	Age in years	Men	Women
Cases with chronic otitis media		27 43	2	–
Cases with incision of the drum	5	17 22, 44, 44, 56	3	2
Total	7	17–56	5	2

(43 %) had a relatively good Et function and could equilibrate an underpressure applied in the middle ear.

Miller reported 54 ears with "normal tympanic mucosa". These ears should be more comparable with the author's material of ears with chronic otitis media. Among the ears in Miller's material with a normal tympanic mucosa 32 cases (60 %) could equilibrate an underpressure, i.e. a higher value than the present author's.

At investigation of the ears by the methods based on application of under- or overpressures in the ear (aspiration and deflation methods) the following curve types could be distinguished:

a) Capacity for equilibrating under- and overpressures applied in the middle ear directly to o-level, (fig. 12)
(o-level = surrounding atmospheric pressure during the investigation with a range of ±2 mm Hg.)
b) Capacity for equilibrating under- and overpressures applied in the middle ear stepwise to o-level (fig. 13)
c) Equilibration only for applied negative and positive pressures exceeding ± 20 mm Hg
d) Equilibration only for applied positive pressure.
e) No capacity for equilibrating pressures.
f) Spontaneous emptying through the Et of applied positive pressure in the middle ear without deglutition

The distribution of types a–e in normal ears and ears with chronic otitis media appears from tables XI and XII.

Table XI. *Type of pressure equilibration in normal ears*

	Type of equilibration		
	Directly to level	Stepwise to 0 level	Number of ears
Aspiration	8	8	36
Deflation	20	16	36

Table XII. *Type of pressure equilibration in ears with chronic otitis media*

	Type of equilibration		Only for pressure differences > ±20 mm Hg	No equilibration	Number of ears
	Directly to level	Stepwise to 0 level			
Aspiration		39	1	56	96
Deflation	13	32	11	40	96

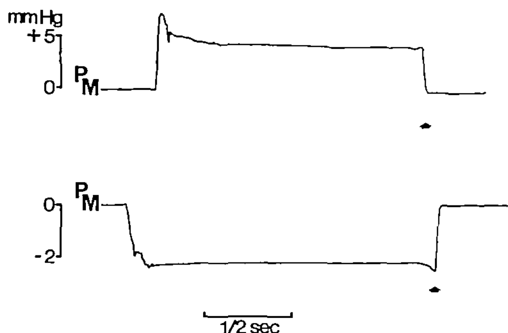


Fig. 12. Recordings in a normal case with ability to equilibrate applied over and underpressures in the ear directly to o-level. Filled arrow indicates deglutition.

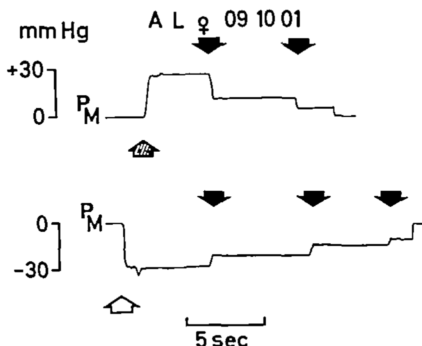


Fig. 13. Recordings in case of chronic otitis media with ability to equilibrate applied over and underpressures stepwise to o-level Filled arrow – deglutition Shaded arrow – application of positive pressure in the ear Hollow arrow – application of negative pressure in the ear

The author thus found that pressure equilibration could take place in two different ways namely directly to o-level and stepwise to o-level (figs. 12 and 13) Among the normal ears the equilibration of underpressures took place directly in 50 % of the cases and stepwise to o-level in 50 % The ears with chronic otitis media which could equilibrate an underpressure did so stepwise in 75 % and directly to o-level in 25 % (Tables XI and XII) At present both types of equilibrations are regarded as normal. Equilibration directly to o-level must imply a very good ventilatory function of the Et whereas the stepwise equilibration may indicate a slightly smaller ventilatory capacity of the Et.

Some ears (Table XII) could only equilibrate high over and underpressures. Miller (1965) reported several cases of this type in his material. These ears are examples of a kind of reduced capacity for equilibrating. In these cases the Et function is dependent on a further factor beyond the normal active muscular opening mechanism. A high pressure difference must exist across the Et to bring about the tubal opening and pressure equilibration.

In some cases spontaneous emptying of air through the Et at application of overpressure in the middle ear takes place at relatively small pressure—below +15 mm Hg. This may mean a tendency towards the condition of patulous tube. This small emptying pressure in certain cases was already observed by Hartmann (1879) At a sufficiently high positive pressure in the middle ear spontaneous emptying of air via the Et normally takes place. In the present investigation this emptying was found to take place between +15 and +40 mm Hg (20–54 cm H_2O) which is in agreement with the values of earlier investigators (Hartmann 1879, Armstrong and Heim 1937) Spontaneous equilibration of underpressure applied in the middle ear without deglutition was only noticed in ears with patulous tubes

INTRATYMPANIC RESIDUAL PRESSURE

Those ears in the author's material which could equilibrate an underpressure generally did so according to the all or none law With few exceptions the equilibration took place to the o-level (Table XIII) A residual pressure (±2 mm Hg = 2 7 cm H_2O) could then be found. This was considered to be normal and was noticed in normal ears as well as in cases with chronic otitis media.

Table XIII. *Intratympanic residual pressures after pressure equilibration in ears with chronic otitis media*

	< 2 mm Hg	2–5 mm Hg	> 5 mm Hg	Number of ears
Aspiration	35	4	1	40
Deflation	48		7	56

Among the 79 ears that could equilibrate underpressures however Miller (1965) found 55 ears (70 %) with residual intratympanic underpressure of from 0 to –5 cm H_2O 24 ears (30 %) had Et thresholds greater than –5 cm H_2O (average threshold of –14.4 cm H_2O) Miller stated that a certain pressure difference across the Et was necessary for equilibration. For this reason Miller regarded the residual pressure after equilibration as an expression of the function of the Et.

The selection of material may explain this difference in the presence of residual pressures in Miller s (1965) and in the author s material. Thus Miller also examined ears with changes of the mucous membranes in the middle ear Such ears were excluded from the present material. It is possible that the mucous membrane factor including swollen mucous membrane and increased secretion was of some importance in Miller s investigation.

PATENCY OF THE EUSTACHIAN TUBE TO INFLATION

Tables IX and X were obtained by pooling the results of the tubal function investigations performed with the different methods based on ear manometry

43 ears (45 %) with chronic otitis media had tubal passage with the graded inflation method at a threshold pressure below 10 cm H_2O At application of an overpressure of up to 25 cm H_2O in the nose 70 ears (73 %) had positive inflation testing

By Politzer s inflation method, passage was obtained in 95 cases i. e. almost in 100 % With this method it is however impossible to determine exactly at what pressure in the nose tubal passage is reached (see fig. 11)

TOYNBEE S MANOEUVRE

At Toynbee s manoeuvre the author found passage through the Et in 83 % of the normal cases (Table IX) This number is a little higher than that of earlier investigators (Zöllner 1942 Thomsen 1958) This may be due to the fact that unlike Zöllner and Thomsen, the author made the investigation after incision of the ear drum. The drum, however probably damps small pressure changes in the middle ear The negative Toynbee tests obtained may be due to an unsatisfactory recording procedure or naturally to a real lack of tubal passage. In ears with chronic otitis media passage with Toynbee s manoeuvre was obtained only in 31 % of the ears (Table X) It is impossible to say how many and which ears with a normal Et function are "lost among the ears with chronic otitis media as assessed by the use of this testing procedure.

COMPARISON OF THE DIFFERENT METHODS

In the analysis of the different tubal function methods it is important to compare the aspiration method and the different inflation methods. In view of the

Table XIV Comparison between aspiration and inflation methods.
Pressure threshold in the nose < 10 cm H_2O

		Aspiration +	Aspiration –	
Inflation 0– cm H_2O	+	37	6	43
	–	3	50	53
		40	56	96

These ears had a positive inflation test at 15 cm H_2O
+ air passage through the Et.
– no air passage through the Et.

Table XV Comparison between aspiration and inflation methods.
Pressure threshold in the nose < 25 cm H_2O

		Aspiration +	Aspiration	
Inflation 0–25 cm H_2O	+	40	30	70
			26	26
		40	56	96

+ air passage through the Et.
no air passage through the Et.

author's opinion on the normal tubal function it seems logical to take the aspiration method as a standard and compare it with the other methods.

Taking ears with chronic otitis media which could equilibrate an underpressure in the ear as a basis it is of interest to see at what overpressure applied in the nose these very ears obtained tubal passage. In the author's material it was proved that if 10 cm H_2O was chosen as an upper limit of overpressure in the nose, there was a very good conformity between positive aspiration testing and positive inflation testing (Table XIV). If on the other hand the upper limit

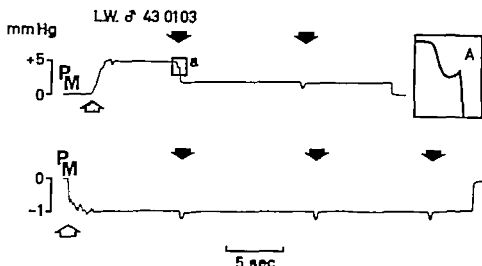


Fig. 4. A case of common cold illustrating negative pressure spikes during ordinary deglutition at close ear manometry. Detail of curve magnified to the right. Filled arrow – deglutition. Shaded arrow – application of positive pressure in the ear. Hollow arrow – application of negative pressure in the ear.

of inflation pressure was kept at +25 cm H_2O a poor conformity was obtained (Table XV). Such a poor conformity was also found on comparison between Politzer's method and a positive aspiration testing. Judging from this comparison between the aspiration and inflation methods there should thus be no objection to taking the upper limit for graded inflation to 10 cm H_2O overpressure in the nose as a clinical standard.

By repeating the investigations the reproducibility of the method could be assessed. With the aspiration method there was no difference between the investigations. With the method of graded inflation there was a very slight difference in the pressure necessary for getting tubal passage. When the cases were divided into different age groups no certain difference was observed between the groups at the various testings. No difference between the sexes was proved.

NEGATIVE DIP PHENOMENON

During investigations of patients with common colds Flisberg, Ingelstedt and Örtegren (1963) observed a phenomenon referred to above as the negative dip phenomenon. This was manifest as a negative pressure spike in the middle ear when the patient swallowed. In the present investigation the phenomenon was found also on several patients without any sign of infection. By using close as well as open ear manometry there were possibilities to study the presence of the phenomenon in certain cases during Toynbee's manoeuvre and ordinary deglutition with open nose. The findings are illustrated in figs. 14 and 15.

In fig. 14 (close ear manometry) it is shown how the tendency of locking

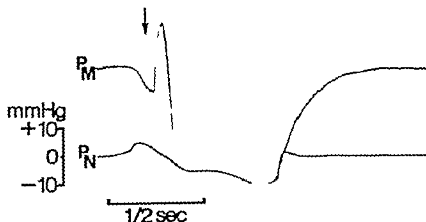


Fig. 15. A normal volunteer without infection showing negative dip phenomenon by performing Toynbee manoeuvre at open ear manometry. The upper curve illustrates pressure changes in the ear. The lower curve illustrates pressure changes in the nose. Arrow indicates the negative dip.

in the Et was overcome by the pressure difference (+5 mm Hg). The negative pressure spike was broken and equilibration was produced. Negative dips without equilibrations were effected at positive as well as negative pressures in the middle ear.

By using open ear manometry a negative dip appeared simultaneously with the positive phase of Toynbee's manoeuvre as illustrated in fig. 15.

EVALUATION OF AIR FLOW DIRECTION

The pressures on both sides of the Et determine the direction of air flow at the tubal opening. With different pressures in the middle ear during closed ear manometry the air flow direction was studied by performing Toynbee's manoeuvre. The results are illustrated in fig. 16.

The pressure variations in the nose during Toynbee's manoeuvre were almost the same in the four examinations. From the figure it appears that

a) An applied moderate overpressure in the middle ear became negative.
b) A high overpressure in the middle ear was not entirely equilibrated to zero.
c) A moderate underpressure became still more negative. The small positive pressure phase in the rhinopharynx that initiated Toynbee's manoeuvre gave however a transient raise of pressure in the middle ear.
d) With a large underpressure a small equilibration towards zero level was obtained.

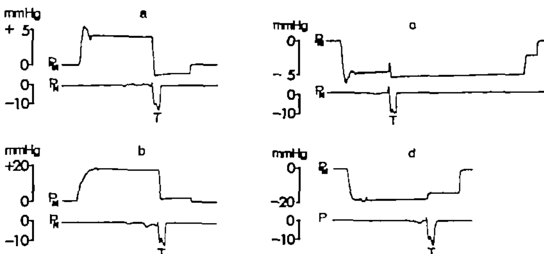


Fig. 16. Example of different air flow directions through the Et by performing Toynbee's manoeuvre in a normal volunteer. After drum incision various pressures were applied in the middle ear. See text. T = Toynbee manoeuvre.

At open ear manometry different air flow directions could be found by performing Toynbee's manoeuvre (fig. 15). The negative spike was broken at the opening of the Et and air was forced into the middle ear as long as the pressure in the rhinopharynx was positive and thus exceeded the middle ear pressure. At the second phase of Toynbee's manoeuvre when the pressure in the rhinopharynx became negative air was sucked out from the middle ear—the air flow had changed direction. If the Et closes during this period a negative pressure remains in the normal middle ear (compare fig. 16 a and c).

COMBINED PRESSURE AND AIR FLOW MEASUREMENTS

At this type of measurements the ears were divided according to the Et function. This division was based on the results of pressure measuring in the ear. Three groups were distinguished:

- Group I cases with capacity for equilibrating underpressure applied in the ear (20 ears)
- Group II cases with no capacity for equilibrating underpressure applied in the ear (19 ears)
- Group III patulous tube cases (7 ears)

The measurements were repeated and the series with highest air flow values for every individual was selected. The air flows in the different testing manoeuvres are given in Tables XXV–XXIX (see Tables pp. 80–82). The maximal

air flow at every pressure difference across the Et was calculated. Corresponding air flow resistance thus means minimum resistance By mean is always meant the arithmetical mean.

The difference (d_i) between two measurements at different examinations of the same patient was used to estimate the variation. This calculation was made from measurements at graded inflation with 30 cm H_2O pressure difference across the Et. The error of the method will be included in this variation.

The coefficient of this variation = $\frac{\sqrt{\Sigma\ d_i^2/n}}{m}$ was then

Group I 17 %
Group II. 6 %
Group III. 10 %
(calculation made in collaboration with F. K. Mats Lörstad)

There were fairly great differences in air flow values among the different individuals of group I and II *obviously due to the fact that the investigations* were made on ears with varying lesions in the middle ear and the Et.

At *graded inflation* group I had air flow resistance values ranging between 5 and 50 cm H_2O/ml/sec. (Tables XVI and XVII)

Table XVI. *Air flow resistances at graded inflation testings*

R cm H_2O/ml/sec	Δp = cm H_2O			Δp = 20 cm H_2O			Δp = o cm H_2O		
	Group			Group			Group		
	I	II	III	I	II	III	I	II	III
0–5	0		6			7	0		5
5–50	9			19			9		1
> 50			0		6	0		10	
Number of ears	20		7	20	6	7	20		7

In 10 ears no passage could be recorded at 1 cm H_2O pressure difference.
In 6 ears no passage could be recorded at 20 cm H_2O pressure difference

Group I. cases with capacity for equilibrating underpressure applied in the ear
Group II. cases with no capacity for equilibrating underpressure applied in the ear
Group III petulous tube cases.

Table XVII *Mean air flow resistances at application of overpressure in the nose* (graded inflation) (Group I)

	R cm H_2O/ml/sec.			
	Δp cm H_2O			
		20	30	40
Mean air flow resistance	25.2	9.3	5.5	
Standard deviation	±13.0	±9.8	±8.3	±5

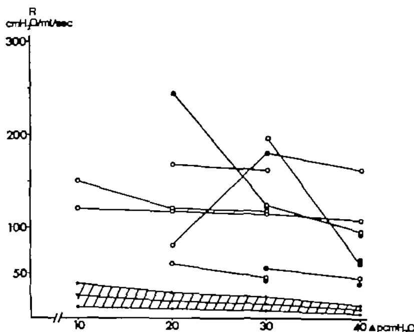


Fig. 19. Air flow resistances of group II tested with graded inflation.

● Testing performed only at one pressure difference across the Et.
○ Testing performed at several pressure differences across the Et.
(For comparison the minimal air flow resistances with standard deviations of group I tested with graded inflation are sketched – shaded area.)
(Primary air flow values of group II are given in Table XXVIII.)

H_2O/ml/sec. (Table XVI) Fig 20 shows the air flows at inflation and aspiration testings of group III at different pressure differences across the Et. Also at aspiration testing it appears from this figure that the resistances were low (below 7 5 cm H_2O/ml/sec.)

A great difference in air flow resistance between the groups at graded inflation testing could thus be demonstrated.

The mean values of air flows in group I at *aspiration testing* are illustrated in fig 21 This test was performed in 13 of the cases. (Two cases with extreme values were excluded from the statistical analysis One of these was the same as the one excluded at graded inflation The calculated air flow resistances in this case ranged between 66 and 120 cm H_2O/ml/sec. The other case had resistance values between 66 and 275 cm H_2O/ml/sec)

From the isoresistance lines drawn in the diagram it appears that there may be a small tendency for the air flow resistance to increase with increasing pressure differences across the Et (compare fig. 17) In Table XVIII the calculated mean resistance values at different pressure differences are given.

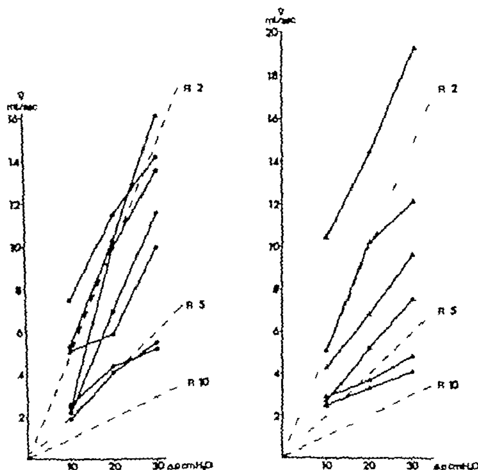


Fig. 20. Air flows in patulous tube cases. In the left diagram testing was performed with graded inflation in the nose (7 ears) In the right diagram testing was performed with applied underpressure in the ear (6 ears) In both diagrams the isoresistance lines showing resistances of 2, 5 and   cm H_2O/ml/sec. are drawn (— — —)

For pressure differences higher than 10 cm H_2O it was also found that the air flow resistances were higher at aspiration testing than at graded inflation testing at the same pressure difference (compare Tables XVII and XVIII)

Application of graded underpressure in the nose in 11 cases of group I gave mean values of air flow resistances as shown in Table XIX. In fig. 22 the mean maximal air flows at different pressure differences are sketched together with calculated isoresistance lines It is seen that there is a small tendency for the air flow resistance to increase with increasing pressure differences. (In the statistical analysis two ears with extreme values were excluded—the same ears as those excluded at aspiration testing In the remaining nine cases the testing was unsuccessful in three and not performed in six cases.)

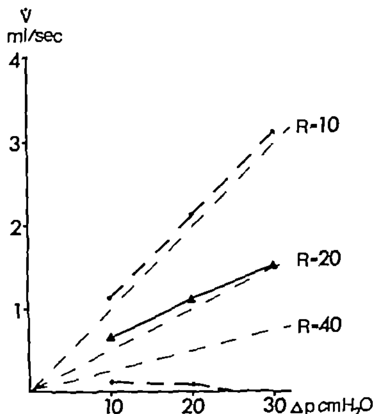


Fig. 21 Mean air flows with standard deviations at aspiration testing of group I. Isoresistance lines showing resistances of 10 20 and 40 cm H_2O/ml/sec. are drawn.

▲——▲ mean air flow
●----● mean air flow ± 1 x standard deviation
— — isoresistance lines

Table XVIII. *Mean air flow resistances at application of underpressure in the ear* (aspiration) (Group I)

	R cm H_2O/ml/sec.		
	Δp cm H_2O		
	10	20	30
Mean air flow resistance	5.2	31.9	38.9
Standard deviation	± 6.3	± 21.1	± 26.2

Table XIX. *Mean air flow resistances at application of underpressure in the nose* (Group I)

	R cm H_2O/ml/sec.		
	Δp cm H_2O		
	10	20	30
Mean air flow resistance	25.6	40.7	53.8
Standard deviation	± 14.9	± 17.4	± 24.8

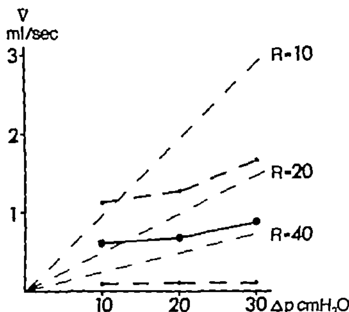


Fig. 22. Mean air flows with standard deviations at application of graded underpressure in the nose of group I. Isoresistance lines showing resistances of 10, 20 and 40 cm H_2O/ml/sec. are drawn.

●——● mean air flow
● - - ● mean air flow ± 1 x standard deviation
— — isoresistance lines

Table XX. *Air flow resistances at various pressure differences across the Et in two cases of chronic otitis media with a good Et function*

	R cm H_2O/ml/sec.			Patient
	Δp cm H_2O			
	10	20	30	
Application of under pressure in the nose	5	49	90	H. H. ♂ 010707
	32	37	58	L. R. ♂ 400513
Application of over pressure in the ear	7.5	11	↓	H. H. ♂ 0 0707
	22	3 ↓	↓	L. R. ♂ 400513

At pressure differences of 20 and 30 H_2O a tendency towards continually open Et arose at application of positive pressures in the ear (indicated by the arrows)

At testing with *application of overpressures in the ear-flow-meter system (deflation method)* the air flow resistances were determined. The resistances were always below the corresponding values at application of graded underpressures in the nose although the air flow direction was the same in both testings. As an example the air flow resistance values are given for two ears with chronic otitis media and with capacity for equilibrating underpressures in the middle ear (Table XX)

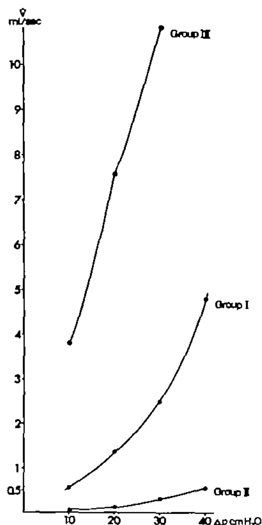


Fig. 23. Mean air flow curves from groups I, II, and III at graded inflation testings. (Primary air flow values are given in Tables XXV XXVIII and XXIX.) Extrapolation of curve from group I has been made—expressed by broken lines.

In respiratory physiology the airway resistance is determined at a fixed air flow rate On principle this can also be done at measurements of the resistance of the Et. However because of the very different air flow rates through the Et of different individuals it is very difficult to compare the individuals as well as the groups of the author s investigation. In fig 23 the mean air flow curves at graded inflation testing of the three groups are drawn. These curves may of course be discussed. Thus in group I the air flow at 40 cm H_2O pressure difference is only calculated from investigations of 7 ears. In group II it was possible to obtain passage only in 2 tubes at 10 cm H_2O pressure difference in 6 at 20 cm H_2O pressure difference in 12 at 30 cm H_2O pressure difference and only in 9 ears was the investigation made at 40 cm H_2O pressure difference. From a statistical point of view even zero values should have been included. However this would have made a comparison impossible

Between the groups I and III a comparison at an air flow of 5 ml/sec. can be made after extrapolation of the curve of group I The calculated resistance values were then

Group I 8.2 cm H_2O/ml/sec.
Group III 2.8 ,, ,,

This apparently means that also in a comparison with this form of calculation the resistance values are lowest among the patulous tube cases.

Between the groups I and II a comparison can be made at an air flow of 0.5 ml/sec. after extrapolating the curve of group I The calculated resistances were then

Group I 18 cm H_2O/ml/sec.
Group II 76 ,, ,,

A great difference in resistance between the groups was thus also shown by this calculation procedure

TYPICAL CASES

In figs. 24–27 examples are given of combined pressure and air flow measuring during testing an ear with chronic otitis media and with an Et capable of equilibrating an underpressure The maximal air flows and corresponding air flow resistances during the different testings appear from Table XXI.

From the case in figs. 24–27 the different testing values have been related to varied pressure differences across the Et in figs. 28 and 29. The diagram in fig 29 illustrates how the air flow resistance increased during aspiration testing and testing with graded underpressure in the nose while the resistances diminished at inflation and deflation testings. As comparison testing values from a patulous tube case are also given in fig 29.

In fig. 30 a case of chronic otitis media with a poorly functioning Et tested with graded inflation is illustrated. The aspiration testing was negative. The pressure difference across the Et necessary to obtain tubal passage was 40 cm H_2O During pressure application in the nose a level of air flow through the Et appeared. This level remained as long as the pressure in the nose remained even after the end of the swallowing phase. From table XXII appears air flow values and corresponding air flow resistances at maximal flow as well as at level flow The air flow resistance value was lowest during the active phase of deglutition.

Testing a case of chronic otitis media with a poorly functioning Et by *Politzer*'s method is illustrated in fig. 31 In this case tubal passage was obtained first at very high inflation pressure in the nose (Δp = 118 cm H_2O) The maximum air

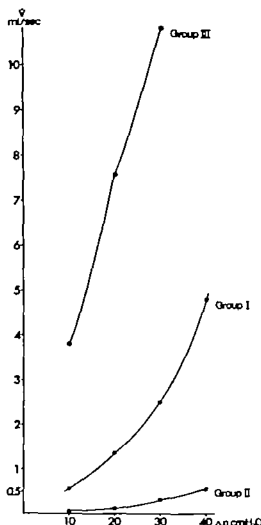


Fig 23 Mean air flow curves from groups I, II, and III at graded inflation testings (Primary air flow values are given in Tables XXV XXVIII and XXIX.) Extrapolation of curve from group I has been made—expressed by broken lines.

In respiratory physiology the airway resistance is determined at a fixed air flow rate. On principle this can also be done at measurements of the resistance of the Et. However because of the very different air flow rates through the Et of different individuals it is very difficult to compare the individuals as well as the groups of the author s investigation. In fig 23 the mean air flow curves at graded inflation testing of the three groups are drawn. These curves may of course be discussed. Thus in group I the air flow at 40 cm H_2O pressure difference is only calculated from investigations of 7 ears In group II it was possible to obtain passage only in 2 tubes at 10 cm H_2O pressure difference in 6 at 20 cm H_2O pressure difference, in 12 at 30 cm H_2O pressure difference and only in 9 ears was the investigation made at 40 cm H_2O pressure difference From a statistical point of view even zero values should have been included. However this would have made a comparison impossible.

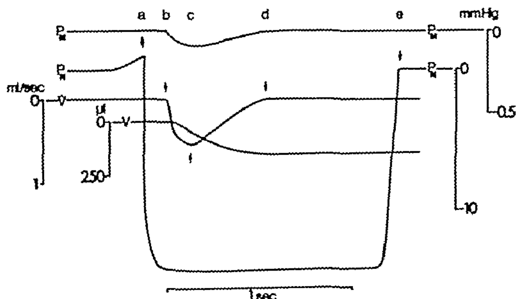


Fig. 25. Combined pressure and air flow measuring by application of underpressure in the nose. The pressure difference across the Et was 20 cm H_2O (14.7 mm Hg). The case was the same as in fig. 24. (For symbols see fig. 24.)

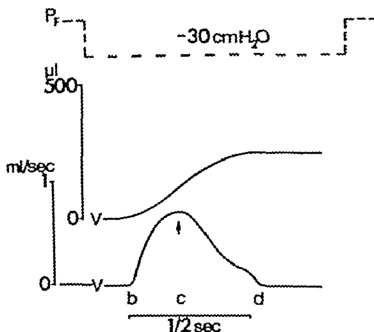


Fig. 26. Combined pressure and air flow measuring by application of underpressure in the ear. The pressure difference across the Et was 30 cm H_2O (22.0 mm Hg). The case was the same as in fig. 24. (For symbols see fig. 24.)

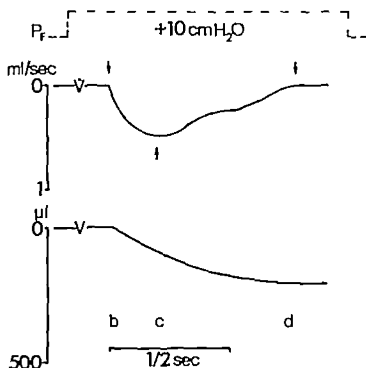


Fig. 27 Combined pressure and air flow measuring by application of overpressure in the ear The pressure difference across the Et was 10 cm H_2O (7.3 mm Hg) The case was the same as in fig. 24. (For symbols see fig. 24.)

Table XXI. *Maximal air flows and corresponding air flow resistances in the case illust ated in figs. 24–27* (italics = calculated air flow resistance values in figs. 24–27)

	V̇ ml/sec.			R cm H_2O/ml/sec.		
	Δp cm H_2O			Δp cm H_2O		
	10	20	30	10	20	30
Aspiration	0.36	0.62	0.70	28	32	43
Inflation	0.39	0	2.0	26	20	15
Underpressure in the nose	3	0.54	51	32	37	59
Deflation	0.45	50	–	22	3	–

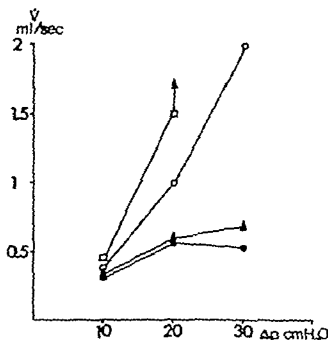


Fig. 28 Air flows through the Et in the same patient as shown in figs 24–27 at different Et testings

●——● Underpressure applied in the nose
○——○ Overpressure applied in the nose (graded inflation)
▲——▲ Underpressure applied in the ear (aspiration)
□——□ Overpressure applied in the ear (deflation)
(Arrow indicates spontaneous emptying)

well as by aspiration testing in a patulous tube case the maximal and level air flows together with the corresponding air flow resistance values were calculated (Table XXIII)

A comparison between air flow resistances at level air flow during graded inflation in a patulous tube case (Table XXIII) and a case with poorly functioning Et (Table XXII) shows much lower values in the patulous tube case

CONSTANT UNDERPRESSURE APPLICATION IN THE MIDDLE EAR

In fig 33 it is shown how the air flow resistance changed when an underpressure of 30 cm H_2O was applied in the middle ear for 25 minutes. The patient was instructed to swallow every fifth minute to equilibrate the underpressure. After 25 minutes there was no equilibration. When the underpressure was released the patient could again equilibrate. The air flow resistance returned successively

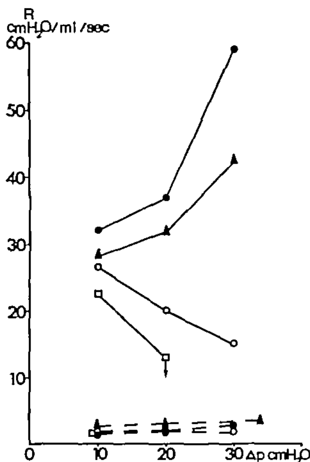


Fig. 29. Air flow resistances of the same patient as shown in figs. 24–27 and in a patulous tube case at different Et testings. (For symbols see fig. 28) Continuous line – case of chronic otitis media (L.R. 400513 ♂) Interrupted lines – patulous tube case (E.A. 081027 ♂)

to a normal value. During the testing of the patulous tube cases however very small changes in the air flow resistance of the Et were obtained during the same procedure.

TUBAL OPENING PERIOD

At air flow measuring with underpressures in the ear the tubal opening time was measured in 13 cases. The times varied between 0.2 and 0.9 sec. with a mean value of 0.36 sec and a standard deviation of 0.21 Every opening time was a mean of 3 measurings (at 10 20 and 30 cm H_2O pressure difference across the Et) Very small variations between tubal opening times in the same patient at varying pressure differences were found.

Earlier investigators found similar tubal opening times. Thus Perlman (1951) found tubal opening times of 0.16 0.20 0.16–0.60 sec. using a sound conduction

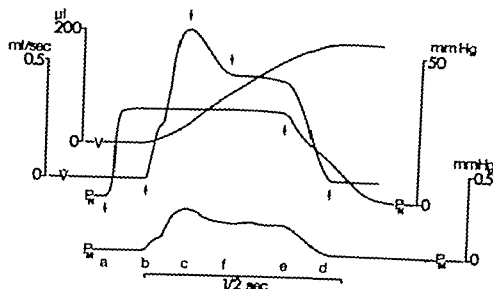


Fig. 30. Recordings from case of chronic otitis media tested with graded inflation. To get tubal passage a pressure difference across the Et of 40 cm H_2O (29.4 mm Hg) was demanded. (For symbols see survey of symbols p. 7) At the arrow indicated by the letter f a level in air flow curve was obtained.

Table XXII. *Maximal air flow and level air flow with corresponding resistances in the case illustrated in fig. 30*

	Graded inflation (Δp = 40 cm H_2O)	
	Maximal air flow	Level air flow
$\dot{V}$ ml/sec.	0.63	.43
R cm H_2O/ml/sec	63	93

technique. Miller (1965) reported values varying between 0.12–0.50 with the mean of 0.24 sec. Aschan (1955) obtained tubal opening times of 0.25 sec. determined from X-ray investigation of the Et with contrast media.

AIR VOLUMES PASSING THROUGH THE EUSTACHIAN TUBE

At aspiration testing, the air volumes passing through the Et in one case with chronic otitis media (capable of equilibrating an underpressure) and in one case with a patulous tube were compared at the same pressure difference (30 cm H_2O across the Et) (Table XXIV) The periods during which the tubes

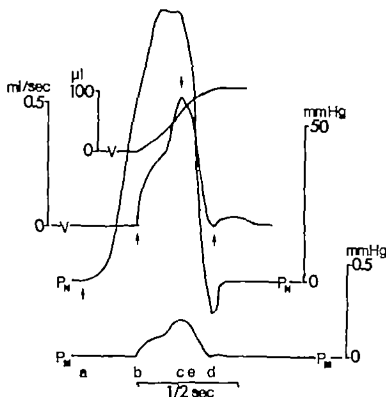


Fig. 31 Recordings from a case of chronic otitis media with a poorly functioning Et only inflatable be Politzer's method. (For symbols see survey of symbols p 7)

were kept open during swallowing in the case with chronic otitis media were 0 5 0 5 and 0 5 sec. and in the case with patulous tube 0 42 0 5 and 0 5 sec. The air volumes were largest in the patulous tube case which means a lower air flow resistance in spite of identical tubal opening times and pressure differences across the Et.

PATULOUS TUBE CASES

Zöllner (1942) pointed out that in cases with chronic otitis media a higher incidence of patulous tube conditions are found than in normal ears. The author's attention was drawn to cases where patulous tube was suspected on anamnestic grounds. Several such cases were found during ear manometry

The ears with patulous tube were investigated in two groups. One of the groups was tested for the capacity for equilibrating an applied underpressure in the middle ear The other group was tested by air flow measuring

In patients with patulous tubes the Et generally closes when the patient is placed in a horisontal position When closure of the patulous tube was effected,

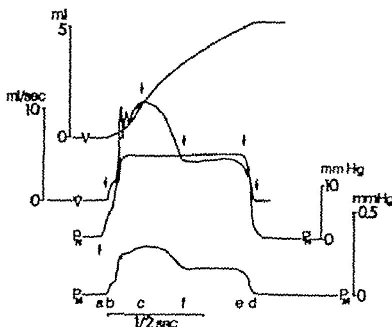


Fig. 32. Recordings from a patulous tube case at testing with graded inflation at a pressure difference of 20 cm H_2O (4.7 mm Hg) across the Et. (For symbols see survey of symbols p. 7.)

Table XXIII. *Air flows and corresponding resistances in a patulous tube case (E. A. ♂ 081027) tested by inflation and aspiration methods.* (Pressure difference across the Et 20 cm H_2O.)

	Graded inflation		Aspiration
	Maximal air flow	Level air flow	Maximal air flow
$\dot{V}$ ml/sec	3	4.4	7.4
R cm H_2O/ml/sec	9	4.8	7

testing with the aspiration method could be performed after ear drum incision. Five of the six cases investigated in this way succeeded in equilibrating under pressure in the middle ear. They all did it directly to 0-level. One patient who had been operated on as a child for a cleft palate could not do this.

The other patulous tube group (7 cases) was investigated by the method for determination of tubal airway resistance. All the resistance values at the different tubal function testings were considerably lower than those for the other ears (see figs. 20–29 and Table XVI).

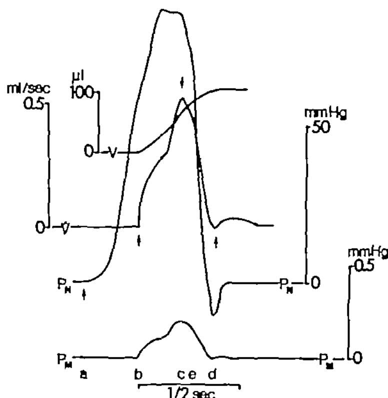


Fig. 3 Recordings from a case of chronic otitis media with a poorly functioning Et only inflatable be Politzer's method. (For symbols see survey of symbols p. 7.)

were kept open during swallowing in the case with chronic otitis media were 0.5, 0.5 and 0.5 sec. and in the case with patulous tube 0.42 0.5 and 0.5 sec. The air volumes were largest in the patulous tube case which means a lower air flow resistance in spite of identical tubal opening times and pressure differences across the Et.

PATULOUS TUBE CASES

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The ears with patulous tube were investigated in two groups. One of the groups was tested for the capacity for equilibrating an applied underpressure in the middle ear. The other group was tested by air flow measuring.

In patients with patulous tubes the Et generally closes when the patient is placed in a horisontal position. When closure of the patulous tube was effected

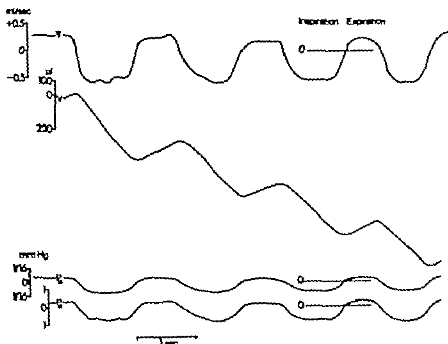


Fig. 34. Recordings from case of patulous tube by combined pressure and air flow measur ings The volumes of air passing th tube are larger at inspiration than at expiration which gives the slope of the integrated curve.

Discussion

The Et is normally closed i.e. the closure forces exceed the opening forces owing to a spring effect exercised by the cartilage and the surrounding tissues. During deglutition, opening may appear allowing a pressure equilibration if there is a pressure difference across the Et. Such a pressure difference is normally a result of the underpressure arising in the closed air space of ear The normal direction of air flow is thus from the rhinopharynx to the ear For this reason the aspiration method devised by the author should be a physiological method for testing the Et function.

In the comparison between normal ears and ears with chronic otitis media a great difference in their capacity for equilibrating underpressures applied in the middle ear was established. Among the ears with chronic otitis media a large number could not perform this while all normal ears could.

The reason why many ears were unable to equilibrate is bound up with factors which regulate the ventilation through the Et. If equilibration does not take place the balance between opening and closure forces has been disturbed. The muscle activity cannot overcome luminal or extraluminal factors which keep the Et closed. There is then a blockage of the Et which may be of a reversible or a permanent type

REVERSIBLE BLOCKAGE

The commonest type is the reversible one which is seen during infections of the nose and the upper airway when swelling of the mucous membrane of the Et takes place preventing normal tubal ventilation. This may result in acute inflammation of the tube and the middle ear During mucosal catarrhs increased secretion may contribute to blockage of the tube, particularly if the secretion is of a very thick and viscous type.

After X-ray treatment of tumours in the nose pharynx or throat serous otitis may appear This depends mainly on mucosal transitory swelling of the tube

It is also well known that mechanical obstruction caused by adenoids often interferes with the Et function. This function mostly becomes normal after removal of the adenoid.

PERMANENT BLOCKAGE

After middle ear inflammations chronic membrane changes may occur in the shape of adherences and thickening of the mucous membrane of the middle

ear and probably also the Et. Different degrees of permanent tubal stenosis may then appear making it difficult for the Et to open effectively

Repeated testings with unchanged results make it possible to state that the blockage in cases of chronic otitis media preventing normal ventilation through the Et depends on stenosis of a permanent type.

While the aspiration method revealed a high number of ears with a poorly functioning Et in chronic otitis media the same result could not be obtained simply by using the inflation method. Passage through the Et could be obtained by using these latter methods (graded inflation and Politzer's method) in all cases if sufficiently high pressures were applied. But simply forcing air through the Et does not reflect its physiological function. The degree of stenosis cannot be exactly assessed even if the threshold pressure for obtaining passage affords some information about the tubal resistance to the air flow

Toynbee's manoeuvre gave negative results also for normal ears Ingelstedt and Örtegren (1963) made studies using Toynbee's manoeuvre and the pressure changes caused by it in the nose and the middle ear They found that an underpressure generally appeared in the middle ear at Toynbee's manoeuvre but positive pressures as well as zero pressures could occur in spite of the fact that there had been a passage. In a number of ears a normal Et function based on Toynbee's manoeuvre may thus go undetected. Therefore this method must be considered as uncertain if the result is negative.

For evaluating the graded inflation method clinically it must be of great interest to compare it with the aspiration method. The author found that cases which could equilibrate an underpressure in the ear also had a tubal passage at graded inflation with an overpressure in the nose below 10 cm H_2O For this reason the author has chosen the upper level of 10 cm H_2O as a standard for clinical evaluation of the Et function with this method. This value is further in good conformity with the results of other investigators (Zöllner 1942 van Dishoeck 1947 Thomsen 1957) In clinical work the graded inflation method could then be regarded as a supplement of the aspiration method.

During ear manometry it was observed that in some cases the equilibration could occur in small stages The volume of the ear-manometer system must be constant during the actual investigations before the ventilatory capacity of the Et from the type of equilibration could be estimated. At the present investigation the measuring system was always the same. The volumes of the air cell system that were determined in cases with chronic otitis media varied within narrow limits (differing very little from values given by Flisberg and Zsigmond 1965) The pressure recording during equilibration may in this way give an estimation of the individual capacity of the Et for ventilating the middle ear Equilibration taking place in small stages seems to indicate greater difficulties in middle ear ventilation One case which could equilibrate an underpressure did so in very small stages at repeated testings. This patient had very high air flow resistance values suggesting real organic stenosis. Myringoplastic surgery had earlier been

performed twice without success Insufficient Et function was almost certainly the reason for the operative failures

The aspiration and the inflation methods afford some information about the ventilation of the middle ear By using principles currently employed in respiratory physiology it was possible to obtain further information about the mechanism which may influence this ventilation.

During the measurements the system must be kept open. This does not reflect the normal state of the middle ear because of the necessary perforation of the ear drum. The ventilatory function of the middle ear however is very complex owing to the interplay of factors i. e the ear drum and the air cell system (Flisberg, Ingelstedt and Örtegren 1963) These factors are mainly eliminated by keeping the measuring system open Therefore the present investigation only concerns the function of the Et.

At very high air flow velocities through a tube the dynamic pressure can increase and obviously reduce the static pressure If then the static pressure becomes lower than the pressure outside an elastic tube wall a tendency to closure of the tube appears.

Yet theoretical considerations and all practical investigations strongly suggest that the dynamic forces are small as compared with the static forces during air flow through the Et. Therefore it is reasonable to assume that the dynamic forces in the Et are negligible A static pressure component, however may affect the Et to a very great extent.

At testing procedures the pressures applied in the nose or ear create varying pressure differences across the Et. When the Et is opened at deglutition this static pressure may influence the walls as a transmural pressure difference If the Et cannot be opened by the muscular forces the static pressure can contribute to opening it. This is exemplified by the Politzer s inflation manoeuvre as well as by overpressure application in the middle ear Though the applied pressures may be unphysiological they provide accessory information about the Et at air flow measurements.

During graded inflation tests reduction of the air flow resistance was regularly found with increasing pressure differences across the Et. By application of graded underpressure in the nose however an increasing air flow resistance could be stated.

The reason for this difference in resistance is the influence of the static pressure on the elastic walls of the Et. Positive pressures in nose or ear give a dilatation of the lumen. Negative pressures on the other hand tend to close the opened Et.

At a sufficiently high overpressure in the nose the Et could even be kept open after the deglutition This means that the static intraluminal pressure counterbalances the closing forces of the tissue The shape of the air flow curve during such inflation tests appears from figs. 30 and 32 Owing to the muscle contraction at the deglutition the Et opens and the air flow starts and rapidly

reaches a peak (phase b–c) When the muscle relaxes the Et tends to close (phase c-f) If however the pressure is greater than the closing forces a flow level is obtained (phase f-e) When the pressure applied in the nose is then reduced the air flow curve shows the closure of the Et.

Capacity for keeping the Et open and getting an air flow level was naturally always seen among patulous tube cases but also in ears with a poorly functioning Et. The pressure needed to get such a flow level was small in patulous tube cases but high in ears with a poorly functioning tube owing to resistance differences.

The long-time effect of underpressure application (–30 cm H_2O) in the middle ear was also studied. (The magnitude of this underpressure was chosen after van Dishoeck's observation (1941) that down to –50 — –60 cm H_2O underpressure could be found in the middle ear.) The Et then locked and equilibration was impossible. The reason may be a sucking effect on the mucous membrane which produces swelling and a transitory blockage at the aural end of the tube. After release of the underpressure the Et opened immediately indicating that a venous congestion was the reason for the locking

The only possibility to get information about the air flow resistance in cases with poorly functioning tubes is forcing air through the Et. Even the incapacity to equilibrate tells us that the Et function is reduced. By the inflation method it was further proved that a high inflation pressure was needed to reach passage. At pressure-flow measurements it was possible to state that these tubes had higher air flow resistances than those found in normal functioning ears These high air flow resistance values seem to be due either to luminar pathological changes i. e. in the mucous membrane or to extraluminal factors i. e. muscular weakness or other tissue changes

THE PATULOUS TUBE STATE

If patients with patulous tubes lie down the Et generally closes Increased venous pressure in the mucous membranes and peritubal tissues is probably the reason for this. In this position all cases examined, except one could equilibrate an underpressure in the ear This finding illustrates a normal muscular opening function of the Et. The equilibration in all these cases took place directly to o-level which means a widely open tube during deglutition.

One patient—earlier operated on for a cleft palate—could not equilibrate underpressure The muscle function of the Et and the soft palate must in that case be considered to be insufficient.

At *testing for determination of the air flow resistances* which was performed in a sitting posture the resistance values were found to be low The Et could however be sucked close at aspiration testing and at application of underpressure in the nose This is in good conformity with the sniffing a procedure

practiced by patients with patulous tubes in order to close the Et and get rid of the symptoms.

NEGATIVE DIP PHENOMENON

The author has earlier (1963) described a phenomenon called the negative dip phenomenon. The observations were confirmed in the present investigation. The dip may appear at deglutition as a negative pressure spike in the closed ear without pressure equilibration. The phenomenon is interpreted as follows: a small rapid pressure change is caused by a volume increase in the middle ear cavity. This volume increase is due to a small separation of the mobile walls of the upper part of the Et probably caused by a tubal muscular effect. The small pressure spikes may counteract the opening of the Et. In ears with big air cell systems and normal drums the effect may be quite negligible. In cases with small air cell systems and drums which lack the damping capacity however the spike may contribute to the locking of the tube.

TUBAL OPENING TIME

By recording of the tubal opening time it is possible to distinguish between an active and a passive period. The active opening period is the time during which the muscle activity can keep the tube open. In fig 24 this period corresponds to phase b–c. In this phase however the inflation pressure must also play a part in the opening act. The active muscular opening period can also be followed by a passive opening phase. In the air flow curve this may be recorded as a level. At inflation tests the tubal opening time may then vary depending on the time during which the overpressure can be kept in the rhinopharynx. At the aspiration test however the active opening period appears more distinct and may sometimes perhaps be shortened by the negative static pressure effect on the tubal walls

AIR VOLUMES PASSING THE EUSTACHIAN TUBE

Because of the prolonged opening time during inflation testings it is possible to force large and varied volumes of air through the Et.

At the *aspiration test, however the opening times were very constant for* every individual. The author compared two cases (one patolous tube case and one case of chronic otitis media) with the same tubal opening times. At the same pressure difference across the Et greater air volumes passing through the Et in the patolous tube case were found indicating a wider tube.

It is a complex problem to reach successful operative results at myringoplastic operations and several factors are at work. One of these factors is the ventilatory function of the Eustachian tube. This function must be normal i.e. the

patient should be able to equilibrate an underpressure in the middle ear From the author s comparison between different clinical tubal function methods it has been made clear that a tubal passage obtained at graded inflation with a pressure less than 10 cm H_2O also means a good Et function.

A poor Et function—at repeated testings—is a very strong reason for avoiding an operation with the present available methods for closing an ear drum perforation.

Other factors essential for the operative result are the size of the perforation at the repair the patient s age and wound healing capacity changes of the structures in the middle ear and possibly also the size of the air cell system (Flisberg, Ingelstedt and Örtegren 1963)

A well developed air cell system—acting as an air chamber—may thus probably reduce the underpressure originating in the air space of the ear and lessen the risks of postoperative complications. The future development will perhaps provide possibilities of enlarging small air cell systems (Flisberg, Ingelstedt and Örtegren 1963, Grahne 1964)

In some of the cases of chronic otitis media the central drum perforation should perhaps be looked upon as the last remaining chance of keeping pressure normal in the middle ear and thereby bring about "healing of the middle ear process. After closure of the perforation a loading of the middle ear may take place, i. e. due to primary tubal blockage or to tubal locking at infection of the upper airways or even locking because of the hydrostatic swelling of the tubal mucous membrane occurring in a recumbent position. Transudation and inflammation of the middle ear may be the consequence It is well known that a serous otitis can occur after blockage of the Et. Such a condition can however be made to disappear by treatment with a plastic tube through the ear drum according to Armstrong (1954) (the method already described by Politzer 1887) thus making artificial ventilation possible for the middle ear

The future follow-up of cases operated on with myringoplastic methods and with preoperatively tested Et function will answer the question whether now available methods for clinical Et function testing are sufficient and whether the limits for these testings are correct.

Summary

The present work was undertaken as a study of the ventilatory function of the Et by different methods and in view of underlying physiological factors. It must be of the greatest importance for microsurgery of the middle ear that the Et function can be accurately estimated before an operation is considered.

The investiation has been restricted to ears with drum perforations or ears where perforations were produced by drum incision.

METHODS WORKED OUT BY THE AUTHOR

EAR MANOMETRY

This method implies that pressure changes in the closed ear—manometer system induced by deglutition are taken as an expression of the capacity of the Et to ventilate the middle ear This method has not earlier been used for testing the Et function.

By application of underpressure in the ear and testing the patient's capacity for equilibrating, the method reproduces normal ear conditions. The procedure has been called the *aspiration method*

By application of positive pressure in the ear the capacity for equilibrating such pressure at deglutition was studied. This procedure has been called the *deflation method.*

EVALUATION OF AIR FLOW DIRECTION

By using a highly amplified manometer system airtightly connected to the external ear canal the direction of air flow at different experimental conditions could be analysed. The system could be closed or kept open The method implies observations of very small air flows through the Et.

COMBINED PRESSURE AND AIR FLOW MEASUREMENTS

This method was based on principles used in studies of respiratory air flow The method has not earlier been used for otological purposes.

After calculation of the air flow ($\dot{V}$) passing through the Et and determination of the pressure difference (Δp) across the tube the air flow resistance (R) could be estimated according to the formula $R = \frac{\Delta p}{\dot{V}}$

OTHER METHODS USED

Politzer's method for obtaining tubal passage
Application of graded over or underpressures in the nose.
Toynbee's manoeuvre.

RESULTS

One hundred and two ears with chronic otitis media and 36 healthy ears were investigated by ear manometry The testings were repeated in the ears with chronic otitis media.

It was found that all healthy ears could equilibrate over as well as under pressures that were applied to the ear

In the series of ears with chronic otitis media only 42 % could equilibrate an underpressure while 58 % could equilibrate an overpressure applied in the ear

The differences between normal ears and ears with chronic otitis media probably depend on tissue factors for example mucous membrane changes with thickening and adherences which prevent opening of the Et in a large number of such ears. These ears would be regarded as unsuitable for tympano- and myringo-plastic surgery with the methods hitherto used.

By testing with different inflation methods (Politzer's method and graded inflation) it was found that at a sufficiently high pressure in the nose a passage through the Et normal or not, was produced at deglutition.

These methods supply information about the capacity to obtain passage through the Et but no data on the function of the Et. At graded inflation the upper pressure limit for getting passage in normal ears was below +10 cm H_2O

In ears with chronic otitis media it was possible to obtain a passage by the inflation method at a pressure threshold below 10 cm H_2O in the same cases that could equilibrate an underpressure applied in the ear This suggests that the upper limit of 10 cm H_2O for graded inflation could be regarded as a sign of acceptable Et function.

As it is impossible to grade the pressure for obtaining passage with Politzer's method, this method must only be regarded as one way of obtaining information about the capacity for getting passage or not through the Et.

By Toynbee's manoeuvre it was found that a great many ears with chronic otitis media but also normal ears lacked passage. This means that this method must be considered uncertain.

Among the 102 cases with chronic otitis media there were 6 ears with patulous tubes. By placing these patients horisontally the Et was closed. Testing with ear manometry could then be performed. Five of these cases could equilibrate an underpressure This supports the assumption that one of the reasons for the condition of patulous tube in these cases was mainly some tissue factor probably bound up with the tubal mucosa while the muscle function was intact.

When there is an increased tendency in the mucous membranes of the Et to stick together attempts to open the Et are often unsuccessful. A slight opening of the aural portion of the Et produced during deglutition gives a simultaneous increase of the closed air volume in the middle ear This has earlier been observed by the author during ear manometry and was called the negative dip phenomenon In the present investigation it was possible to verify the presence of this phenomenon. The negative pressure spike was further found also in normal ears with no sign of infection and probably without any marked tendency in the mucous membrane to be glued together

Measuring of the air flow resistance of the Et was performed in 39 ears with chronic otitis media 2 ears with chronic otitis media with patulous tubes and 5 ears with symptoms of patulous tube with intact ear drums. In the last cases incision of the drum was performed. The presence of patulous tube was verified by ear manometry

The cases were divided into 3 groups

Group I. Cases which could equilibrate an underpressure in the middle ear (20 ears)
Group II Cases which could not equilibrate an underpressure in the middle ear (19 ears)
Group III. Cases of patulous tube (7 ears)

By testing with graded inflation the resulting air flow resistances were found to be different in the various groups Group I had resistance values between 5 and 50 cm H_2O/ml/sec Group II values between 50 and 200 cm H_2O/ml/sec. Group III values below 5–6 cm H_2O/ml/sec.

During the inflation testing of group I it was found that the air flow resistances diminished with increasing pressure differences across the Et.

During application of underpressure in the ear (aspiration testing) or application of underpressure in the nose the air flow resistances were found to increase slightly with increasing pressure differences across the Et.

The resistance changes seem to be due to the influence of static pressure on the tubal walls. At graded inflation testing a dilatation of the Et appears while at underpressure application in the ear or the nose a certain narrowing of the lumen may take place

During air flow from the middle ear to the rhinopharynx it was shown that the air flow resistances at application of underpressures in the nose were higher than those at testing with application of positive pressure in the ear

By exposing the middle ear to underpressure (– 30 cm H_2O) it was possible to prove that the Et could be locked for air passage at deglutition in certain ears. After 5–10 minutes the locking had disappeared. This indicates that the reason

was venous congestion of the mucous membranes. The investigation simulated pathological conditions in the ear

The duration of the air flow period was taken as the tubal opening time when aspiration testings were performed. The time values were very constant for every individual but differed widely from one case to another (mean value 0.36 sec. standard deviation 0.21)

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Table XXV *Primary air flow values at the testing of group I with application of overpressure in the nose* (graded inflation)

Patient		V ml/sec.			
		Δp cm H_2O			
		0	20	30	40
I.S	3 1220 ♀	0.22	0	5.0	–
G.B	460906 ♂	1.25	2.30	3.6	5.4
J.A.	491028 ♀	0 42	1.0	5	3.7
H.A.	140219 ♂	0.66	1 50	2.5	5.0
A.H.	200907 ♂	0.66	10	.0	–
L.R.	400513 ♂	0.39	1.0	2.0	–
L.N	510808 ♀	55	.40	2.9	–
S.G	60826 ♀	0.22	0.80	1.9	–
T.L.	25 015 ♂	0.2	0.50	0.8	2.0
S.E.O	310524 ♂	0.28	0.53	.0	–
H.H.	010707 ♂	0 58	1 30	2 3	–
V.S.	380322 ♀	0.37	0.65	1 5	–
M.J	38 207 ♀	1 50	3 00	5.8	8 5
H.B	990627 ♀	0.26	0.80	5	3.2
S M.	200915 ♀	0.28	0.80	3	–
L.O	200904 ♀	1.80	3 30	3 8	5.8
K.N	530109 ♀	0.33	0.75	1 3	
B.A.	45 016 ♀	33	.92	2.0	–
A.J	450426 ♀	0.72	50	4.5	–
M.B F	30809 ♀	0.07	0.1	0.20	0.24
Mean air flow		0.58	38	2.5	4 8
Standard deviation		±0.46	±0 84	±1.2	±2.1

excluded in the statistical analysis.
testing not performed.

Table XXVI. *Primary air flow values at the testing of group I with application of nder pressure in the nose*

Patient			V ml/sec.		
			Δp cm H_2O		
			0	20	30
J.A.	491028	♀	–	0.42	0.50
A.H.	200907	♂	0.20	0 30	–
G.B.	460906	♂	.66	0.66	66
L.R.	4005 3	♂	0 31	0 54	0.51
L.N	510808	♂	0 59	0.79	60
S G	80826	♀	27	0.42	0.42
S.E.O	3 0524	♂	0.29	0.37	0.48
H.H.	0707	♂	66	0.41	33
M.J	38 207	♀	.80	2 20	2 50
*T.L.	25 0 5	♂	0.05	0.05	–
M.B.F	230809	♀	0 1	0.17	0.20
Mean air flow			0.60	0.68	0.87
Standard deviation			±0.52	±0.59	± 77

excluded in the statistical analysis.
no passage reached.

Table XXVII. *Primary air flow values at the testing of group I with application of under pressure in the ear* (aspiration)

Patient			V ml/sec.		
			Δp cm H_2O		
				20	30
I.S	31 220	♀	0.18	0.27	0.35
G.B	460906	♂	0.83	1.50	.90
J.A.	491028	♀	0.42	50	0.59
H.A.	402 9	♂	.1	.90	2.40
A.H.	200907	♂	0.25	50	0.66
L.R.	4005 3	♂	0.36	62	0 70
L.N.	510808	♀	53	0.85	1.20
S.G	80826	♀	.24	37	0.41
S.E.O	3 0524	♂	.28	0.48	0.55
H.H.	0707	♂	.00	40	70
M.J	38 207	♀	90	3 80	6 00
*T.L.	5 5	♂	0 5	0.	0
M.B.F	230809	♀	0.15	0.23	.25
Mean air flow			64		50
Standard deviation			± 52	± 04	±1.64

excluded in the statistical analysis

Table XXV *Primary air flow values at the testing of group I with application of overpressure in the nose* (graded inflation)

Patient			$\dot{V}$ ml/sec.			
			Δp cm H_2O			
			10	20	30	40
I.S	311220	♀	0.22	2.0	5.0	–
G.B	460906	♂	1.25	2.30	3.6	5 4
J.A.	491028	♀	0.42	1.0	2.5	3.7
H.A.	140219	♂	0 66	50	2.5	5 0
A.H.	200907	♂	0.66	1 10	1 9	–
L.R.	4005 3	♂	0.39	1.0	0	–
L.N.	510808	♀	0.55	1.40	2.9	–
S G	80828	♀	0.22	0.80	1 9	–
T.L.	251015	♂	0.21	0 50	0.8	2.0
S.E.O	310524	♂	28	0.53	.0	–
H.H.	010707	♂	0.58	1.30	2.3	–
V.S	380322	♀	0 37	0 65	5	–
M.J	381207	♀	1 50	3 00	5.8	8 5
H.B.	990627	♀	0.26	.80	1 5	3.2
S.M.	2009 5	♀	0.28	0.80	1 3	–
L.O	200904	♀	1.80	3 30	3.8	5.8
K.N	530109	♀	0.33	0.75	1 3	–
B.A.	451016	♀	0 33	0 92	2.0	–
A.J	450426	♀	0 72	2.50	4.5	–
M.B.F	230809	♀	07	2	0.20	0.24
Mean air flow			0 58	38	2.5	4 8
Standard deviation			± 46	± .84	± 1 2	± 2.

excluded in the statistical analysis.
testing not performed.

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VENTILATORY STUDIES ON THE EUSTACHIAN TUBE

A Clinical Investigation of Cases with Perforated Ear Drums

BY

KNUT FLISBERG

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Contents

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The author's attention has been drawn to the importance of a thorough knowledge of the Eustachian tube function for modern middle ear surgery Thanks to available antibiotics and a better technique there are now better possibilities to operate successfully for improvement of hearing in cases of chronic otitis media A perfect and lasting operative result with a normal middle ear function depends however on several factors. Among these the Eustachian tube function is an essential one. Pre-operative examination of the tubal function must be regarded as no less important than testing of the hearing function. The Eustachian tube function however has not always been satisfactorily considered at the pre-operative assessment of the patient since the methods for studying this function have not been suitable In spite of an excellent surgical technique, an operation may fail because of a poor Eustachian tube function.

On the whole the anatomical and histological structure of the Eustachian tube has been well known for a long time The physiological and pathophysiological conditions however have been more difficult to evaluate and have for this reason been vividly discussed.

The functions that have been attributed to the Eustachian tube are *ventilation drainage* and *protection* of the middle ear By the ventilatory function is meant the capacity of the Eustachian tube to admit air passage into the middle ear to keep pressure equilibrium on both sides of the ear drum. Under normal conditions this ventilatory function of the Eustachian tube is probably the most important of the functions referred to.

The Eustachian tube must be regarded as part of a functional unit that also consists of the middle ear the air cell system and the ear drum. An attempt to analyse all these factors simultaneously with regard to each other is a very complex enterprise The author has restricted his examination only to an investigation of the ventilatory function of the Eustachian tube.

Earlier methods for pre-operative assessment of the ventilatory function were based on observations as to whether a pressure controlled or uncontrolled and applied in the rhinopharynx during swallowing, caused passage of air to the middle ear In such tests air is *forced* into the middle ear

From a physiological point of view however air is *sucked* into the middle ear when the Eustachian tube opens. The reason for this is that normally the pressure in the air space of the ear continuously falls slowly because of uptake

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of gas from the middle ear From the point of view of normal physiology therefore it would appear more suitable to test the Eustachian tube by a method based on application of underpressure in the ear and to study the ability of the ear to equilibrate this underpressure Such a method has been described by Flisberg, Ingelstedt and Örtegren (1963) (preliminarily read before the Swedish oto-rhinolaryngological Society in December 1961) and called the aspiration method.

Anatomically the Eustachian tube and the middle ear may be considered to be a part of the upper airway Since ventilation of the middle ear takes place through the Eustachian tube there are physiological similarities with the upper airway but also of course great differences. Thus ventilation of the middle ear occurs only during the short moments when the Eustachian tube is opened and then only for equilibration of pressure As the Eustachian tube functions as an organ ventilating the middle ear it is obvious that its function may be discussed according to principles used in respiratory physiology During the opening period of the Eustachian tube the same principles as those used in the airways would then be applicable

The aim of the present investigation which was restricted to ears with perforated ear drums was

1 to work out refined methods for evaluation of the ventilatory function of the Eustachian tube

2 to apply the new methods to normal ears ears with chronic otitis media and ears with patulous tubes

3 to compare the new methods with some earlier methods for evaluation of the Eustachian tube function and judge their usefulness in clinical work with special reference to pre-operative assessment of tubal function.

Survey of symbols

Parts of the system of the Eustachian tube nose and ear

Et – Eustachian tube
M – Middle ear
N – Nose (including rhinopharynx)

Measured quantities

V – volume expressed in millilitre (ml) or microlitre (
P – pressure relative to atmospheric pressure expressed
mm Hg
P_N – pressure in nose
P_M – pressure in middle ear
P_F – pressure generated in middle ear system by a f
Δp – change in pressure
$\dot{V}$ – air flow expressed in millilitre per second (at
expressed in millilitre per minute)

Derived quantity

R – air flow resistance the ratio Δp (cm H_2O) to simultan

In figures illustrating air flows the following symbols were u

a – starting of pressure application
b – opening of the Eustachian tube (at deglutition)
c – point of maximum air flow through the Eustachian tu
d – closure of the Eustachian tube
e – end of pressure application
f – beginning of level in air flow

Structure as a basis for the Eustachian tube function

This description only concerns data of importance for the present investigation [For detailed reviews see Zöllner (1942) Graves and Edwards (1944) Ter racol (1949) Perlman (1951) Aschan (1955) and Berendes et al (1965)]

The Et is a tubular S-shaped organ of 31–38 mm of length (Graves and Edwards 1944) connecting the middle ear with the rhinopharynx. It consists of an osseous part—the posterolateral third which can be considered as an extension of the middle ear and a cartilagineous part which constitutes the anteriomedial two thirds. The connection between the cartilagineous and osseous parts is called the isthmus and constitutes the anatomically narrowest part of the Et towards which the tube narrows hourglass wise

CARTILAGE

According to the general description a cross section of the tubal cartilage forms a shepherd s crook with a medial bigger and a lateral smaller part. In the groove between these cartilagineous lamellae is located the real mucous membranous tube which is slightly movable. The medial wall of the Et consists of the big cartilage lamella Laterally the small lateral cartilage is continued by a tendon disc which constitutes the main part of the lateral wall and by the fascia salpingopharyngeus. The floor of the Et consists of a fascia running to the levator veli palatini muscle Between the walls of the mucous membranous tube and these fascias there is tissue consisting of fat cut through by streaks of connective tissue

The cartilage is mainly of a hyaline structure but also contains elastic elements. The elastic component is considerably bigger in adults than in children (Aschan 1954) Zöllner (1942) and Aschan (1954) have also pointed out that the cartilage is richest in elastic tissue at the point where the medial and lateral cartilage parts are connected. The perichondrium and the submucosa have also a high proportion of elastic fibres (Guild 1955) in that part of the Et This structure with a concentration of elastic fibres in and around the upper part of the tubal cartilage makes possible the spring effect which causes the closure of the Et The closing mechanism probably operates quite passively firstly because of this spring effect of the cartilage and secondly because of the elasticity and pressure exerted by the surrounding tissues (Zöllner 1942 Guild 1955) According to Perlman (1939) the muscle tonus also plays a part in the closing mechanism.

Opinions have been divided as to the normal condition of the Et. A summary of the views on this question has been given by McMyn (1940)

Nowadays it is established that the Et is normally closed at rest and that there is no active muscular closing mechanism.

The tubal opening, however takes place above all at deglutition by muscle activity The muscles connected with this opening mechanism of the Et consist of the tensor veli palatini muscle the levator veli palatini muscle and the salpingopharyngeus muscle The Et is opened mainly by contraction of the tensor veli palatini muscle. This muscle takes its origin from the base of the skull between the spina angularis of the sphenoidal bone and the pterygoid process from the lateral lamella of the tubal cartilage and from the fascia salpingopharyngeus. Its tendon passes round the hamulus os pterygoideus where it is partly attached, and ends in the aponeurosis of the soft palate. The opening function of this muscle was described for the first time by Valsalva (1704) (cited from Macbeth, 1960) and verified by experiments on dogs by Politzer (1861) and Rich (1920)

The opening is effected by pulling of that part of the tensor veli palatini muscle which takes its origin from the lateral cartilage. The cartilage then unrolls a little and the lumen can be opened. Probably there is also a certain indirect muscular influence on the mucosal tube from the connective tissue streaks that cut through the tissues surrounding the tube (Zöllner 1942)

By direct stimulation of the tensor veli palatini muscle in dogs Holborow (1962) proved that this muscle was responsible for the opening of the Et. The opening was made impossible by cutting the muscle.

The levator veli palatini muscle takes its origin from the inferior surface of the petrous portion of the temporal bone anterior to the orifice of the carotid canal. It passes under the Et parallelly with the tubal cartilage The levator veli palatini muscle ends in the soft palate where the muscles from both sides are connected with each other

The salpingopharyngeus muscle takes its origin from the medial and inferior corner of the tubal cartilage and branches out in the muscles that form the lateral wall of the pharynx.

According to McMyn (1940) Zöllner (1942) McGibbon (1942) and Aschan (1955) the levator veli palatini and possibly also the salpingopharyngeus muscle may have a synergistic effect with the tensor veli palatini muscle in the opening mechanism of the Et when contracting. The levator veli palatini muscle would then assist in the opening process by elevating the medial cartilage

INNERVATION

The motor innervation of the tensor veli palatini muscle has been studied and elucidated by Politzer (1861) and Rich (1920) They have shown on dogs that this muscle is innervated by the third branch of the nervus trigeminus via the

otic ganglion There are different views on the motor innervation of the other muscles. Thus Graves and Edwards (1944) consider that the levator veli palatini muscle is supplied by the vagus nerve whereas Rich (1920) is of the opinion that the vagus or the accessorius nerve is responsible for the innervation of this muscle.

The sensory nerve supply of the Et takes place either via the trigeminal nerve or the glossopharyngeal nerve Thus Erickson (1935) found complete anesthesia of the Et following intracranial section of the glossopharyngeal nerve. Dandy (1927) and Stookey (1928) pointed out that the pharyngeal orifice of the Et forms a part of the area of supply of the glossopharyngeal nerve. According to Graves and Edwards (1944) the pharyngeal tubal orifice may also be innervated by the trigeminal nerve This finding may be explained by the pharyngeal nerve supply from the sphenopalatine ganglion.

According to Terracol (1949) the vegetative innervation of the Et proceeds from the trigeminal branches via the sphenopalatine and otic ganglions By way of comparison it may be mentioned that the sphenopalatine ganglion also sends sympathetic and parasympathetic branches to the mucous membranes of the nose (Larsell and Fenton 1936)

MUCOUS MEMBRANE

The mucous membranes forming the real lumen of the Et consist of a ciliated columnar epithelium of the same type as that in the upper airway (Eggston and Wolff 1947) and a tunica propria. This tunica propria is dividable into three layers basement membrane lymphoid layer and glandular layer The mucous membrane is folded by rugae of the same type as in the gut (Moos 1874 Eggston and Wolff 1947) Citelli (1905) (cited from Graves and Edwards 1944) points out that because of intervening layers of lymphatic tissue the lymphoid layer is best developed in children and less so in adults Aschan (1954 1955) however found no lymphatic tissue in the tubal mucous membranes. According to Polvogt and Babb (1940) there is an elaborate lymphatic and vascular network in the lymphoid layer which is particularly pronounced in children. This may be partly responsible for the rough character of the mucous membrane

Because of the character of the mucous membrane with its mucous glands the inner surfaces of the Et easily stick together At the opening of the Et this occlusion must be broken As early as 1869 Cleland pointed out that a film of moisture occludes the tube The surface tension may be of some importance in this mechanism so that the mucous membranes in the cartilagineous part of the Et are glued together (Flisberg, Ingelstedt and Örtegren 1963) The character of the secretion must play a certain rôle in the process. McMyn (1942) Aschan (1955) and Flisberg Ingelstedt and Örtegren (1963) discuss the possibility that at the contact between the moist mucous membrane surfaces the capillary power must be of importance as a factor in the closure of the Et.

Normal ventilatory function of the Eustachian tube

From a ventilatory point of view the normal Et function is to keep a pressure equilibrium between the atmosphere and the middle ear However there may normally exist a slight underpressure in the middle ear depending above all on the uptake of gas from the middle ear This procedure is a complex one and depends in its turn on i. a. the state of the mucous membrane and its area. The pressure drop must of course also depend on the volume of air in the system.

The mucosa of the air cells is normally less vascular than the mucosa of the middle ear During operation on normal ear cases it is easy to observe that the mucous membrane lining the *promontorium* and the ear drum seems to be much more abundantly vascularized than the thin mucosa lining the accessory air space. In Rauber Kopsch (1955) it is also pointed out that the mucosa of the mastoid cells is poorer in blood vessels Therefore the main resorption of gas would take place from the middle ear mucosa. An underpressure because of gas resorption would therefore originate *slower* in ears with big than in ears with small air cell systems.

The equilibration of pressure taking place through the Et means that air is sucked into the ear i. e. an aspiration of air takes place. This equilibration nor mally occurs mainly at swallowing According to Graves and Edwards (1944) the frequency of deglutition in adults is once per minute when awake and once every fifth minute when asleep (in infants more frequently) The Et does not, however open at every deglutition (v Gyergyay 1932 Perlman 1951 Aschan 1955) The time during which the Et is open and equilibration can take place is very short. According to Perlman (1951) Aschan (1955) and Miller (1965) the time varies between 0 12 and 0 60 seconds

It is a wellknown fact that the Et may function like a valve mechanism. Thus an underpressure in the middle ear or an overpressure in the atmosphere usually requires an active tubal opening for pressure equilibration. A high overpres sure in the tympanic cavity on the other hand, may easily force the Et open (Hartmann 1879) Normally all equilibrations take place at deglutition without difficulty and without being noticed. During certain conditions, however also a normally functioning Et can be thrown out of gear Such pressure changes can occur during flying when extreme pressure variations may take place very rapidly If in such circumstances the overpressure in the atmosphere becomes too high a locking of the Et can take place. It is then impossible for the muscles of the tube to open it since the fibro-cartilagineous part of the Et that is elastic and yields readily to pressure (Bryant 1907) collapses completely Zöllner (1942) has pointed out that the fossa Rosenmülleri is of importance in this mechanism. According to Armstrong and Heim (1937) such locking of the

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Et—from the outside—occurs at a relative overpressure in the atmosphere exceeding +90 mm Hg The phenomenon which is a "man-made problem has been illustrated by McGibbon (1942) with the aid of an ear Et model and called "pressure occlusion

Ventilatory function during pathological conditions

The tissue factors causing passive closure of the Et counterbalance the muscular opening mechanism. The concept tissue factors covers the elasticity of the cartilage the properties of the mucous membrane, and the pressure and elasticity of the tissues surrounding the Et.

A disturbance in the balance between opening and closure mechanisms gives a disturbed function in the Et.

A normal muscle activity is of vital importance for the opening of the Et and the ventilation of the middle ear This is best shown in cases where the muscles of the palate and the Et do not function normally i. e. in children with cleft palates In these cases hearing impairment of a conductive nature is often found in more than 50 % (Holmes and Reed 1955, Drettner 1960 Holborow 1962) This hearing impairment is caused by malfunction of the muscles of the Et (Gaines 1940 Holborow 1962) which cannot effectively open the Et for ventilation of the middle ear

Hearing impairment has also been demonstrated after occlusion of the Et by placing a small inflatable rubber balloon in the nasopharynx (Lock 1942 Herberts 1948)

By pneumophone measuring in the ear canal van Dishoeck (1941) found underpressures in the middle ear down to -60 cm H_2O He concluded that the reason for the underpressure was a high resistance of the Et.

A change of the conditions of the tissue factors may give function disturbances which in principle may be of two kinds either the tube cannot open or it is continually open

It is wellknown that in the middle ear adherences and thickening of the mucous membranes can occur after infections. This may also probably take place in the Et. As a result of these changes stenosis of the tubal lumen can appear In cases of longstanding infection it is also possible that more far reaching changes in cartilage and tissues may occur Difficulties at tubal opening and equilibration of originated underpressures in the middle ear may be the consequence. There is then a certain danger of chronic lesions to the middle ear Of these lesions chronic otitis media is the most serious.

It seems generally accepted that inflammatory middle ear diseases occur more commonly in ears with a poorly pneumatised air cell system (Diamant 1940) The connection between the Et function and the pneumatisation of the bone of the ear is however not clear Ojala (1957) has shown that the pneumatisation of chicken humerus can be checked by permanent occlusion of the foramen pneumaticum together with a slight inflammatory process in the air space of

the bone *It is not clear whether the circumstances are the same after occlusion* of the Et in man

If the tubal opening is impossible however the result is a negative pressure in the middle ear

Bezold (1883) was of the opinion that a non-inflammatory transudation takes place in the middle ear after tubal blockage the so-called ex vacuo theory Opinions contrary to the ex vacuo theory have been put forward by e g Zöllner (1942) and Senturia et al. (1962) who are of the opinion that serous otitis must be looked upon as an inflammatory or allergic middle ear disease and is very *seldom produced by* vacuum.

The occlusion of the Et can be compared with a blockage of a bronchus of the lung In the lung this means atelectasis of the lung, a lobe or a part of a lobe—in the ear atelectasis of the whole middle ear and air cell system.

Flisberg, Ingelstedt and Örtegren (1963) and Flisberg (1964) showed that at falling negative pressure in the middle ear the normal ability to aspire" is first more and more impaired while inflation still takes place easily (This was in fact suggested by E. P Fowler (1920) who observed vacua in the middle ear varying between 10–15 mm Hg, though in tubes which opened even at gentle inflation) This form of tubal "locking could be seen in normal subjects at high negative pressures in the middle ear but at very moderate middle ear negative pressures during common cold

Flisberg, Ingelstedt and Örtegren (1963) further observed negative pressure spikes in the ear produced by swallowing especially in cases of common cold during the locking period This phenomenon (called the negative dip phenomenon) must be produced by an increase of the ear space volume Such an increase can be due to a separation close to the isthmus of the mucous mem branes that are glued together

It seems quite clear that the condition of the mucous membrane must be of great importance for the air passage through the tube. Thus oedema of the membrane as well as vascular factors should be essential. The importance of the vascular factor for the function is clear from the fact that a continually open Et—patulous tube—generally closes after the patient is placed horisontally (Perlman 1939 Moore and Miller 1951) In this situation the hydrostatic pressure in the mucosal vessels is raised and the membranes swell so that the Et closes. During inflammatory conditions the lumen is also closed because of increased secretion vascular congestion and oedema

The cause of the patulous tube state *is considered to be* both a tissue factor and a muscle factor Owing to loss of tissue around the tube in connection with marked loss of weight in cases of debilitating disease (Moore and Miller 1951) patulous tubes can appear (Ostmann s theory of fat atrophy of the tube 1893) Handl (1959) pointed out that after retrogasserian neurectomy atrophy of the mucous membrane of the same side of the nose may be combined with a patulous tube This would then be due to trophic disturbances of the mucous membrane of the Et.

According to Perlman (1939) many cases of patulous tube are seen among

patients operated on by retrogasserian neurectomy because of trigeminal neuralgia. Perlman believes that a lack of tonus of the muscles that affect the Et (tensor veli palatini muscle) and are supplied by the fifth nerve is the principal factor in producing the clinical entity

Earlier methods for evaluation of the ventilatory function of the Eustachian tube

A detailed review of methods giving and indicating tubal passage has been given by Ingelstedt and Örtegren (1963)

The present investigation covers ears with a permanent ear drum perforation or ears where a perforation was produced by drum incision. This account will be restricted to methods that can be used when there is perforation of the drum.

The methods based on application of contrast media for X-ray studies (Rees Jones 1941 Welin 1947 Aschan 1954 Compere 1958) or application of tracer solution to the middle ear (Rogers Kirchner and Proud 1962) must be regarded as unphysiological from the ventilatory point of view These methods supply information on the pathological conditions of the Et and elucidate the ability of the Et to drain the middle ear They do not reflect the normal air ventilation

METHODS GIVING TUBAL PASSAGE

UNCONTROLLED PRESSURE CHANGES IN THE RHINOPHARYNX

a) *Politzer's method*

In the middle of the 19th century *Politzer* introduced a method of testing the passage through the Et by forcing air from the nose into the ear For this purpose a bag was used which could be placed airtightly to one nostril and then compressed so as to raise the pressure in the rhinopharynx at swallowing Another possibility was to force air into the middle ear through a tubal catheter introduced into the tubal pharyngeal orifice

b) *Toynbee's manoeuvre*

Toynbee pointed out (1853) that a dump feeling depending on a pressure change in the ear appears at swallowing with the nose closed. The feeling does not disappear before the next act of swallowing This method for bringing about pressure changes in the middle ear has been used as a function test of the Et by Zöllner (1942) and Thomsen (1958)

CONTROLLED PRESSURE CHANGES IN THE RHINOPHARYNX

Hartmann (1870) produced a controlled overpressure in the rhinopharynx by blowing a continuous air flow through the nasal cavity An estimate of the pressure at which the Et opened was then given This principle has later been

used by Zöllner (1942) Perlman (1943) Thomsen (1955) Oltersdorf (1962)
Ingelstedt and Ortegren (1963) worked out a pressure device for producing a constant square pressure wave in the rhinopharynx. The pressure at which tubal passage appeared was then determined.

METHODS INDICATING TUBAL PASSAGE

Indication of tubal passage during middle ear ventilation in cases with a perforation of the drum must be made either with recording of sound or with recording of pressure variation in the ear canal.

a) The simplest form of sound recording is auscultation in the ear canal, at which the sound changes produced at air passages through the Et or at application of sound in the nose can be heard by the investigator (Toynbee 1853, Lucae 1867 von Gyergyay 1932 Zöllner 1942) Perlman (1943) used this principle but completed it by threshold pressure produced in the nose.

b) Objective recording of a sound conducted into the nose and transmitted to the ear canal at the tubal opening was made by Perlman (1951)

c) For recording of pressure changes in the ear canal Politzer (1861 1862) used an ear canal manometer (a droplet moving in a pipet) The same method has been used by Woyatcheck (1908) and Terkildsen (1956) A Marey capsula was used by von Gyergyay (1932) and Oltersdorf (1954)

d) For indicating tubal passage Juganov (1960) Oltersdorf (1962) and Ingelstedt and Ortegren (1963) used pressure transducers connected to the ear canal

e) Ingelstedt and Ortegren (1963) described a flow rate meter device for indicating tubal passage.

f) By determination of pressure changes in a rigid closed tank of known volume connected to the external ear canal Ingelstedt and Ortegren (1963) measured the volumes of air that passed the Et. They performed the investigation with their ear-snorkel-pressure chamber technique and could determine the air volumes passing through the Et in both directions

Earlier results

PRESSURE VARIATION IN THE NOSE

As regards controlled pressures in the rhinopharynx during swallowing it is possible to quantitate the pressure necessary for obtaining tubal passage. Such investigations have earlier been reported only after testing ears with intact ear drums. The results of these investigations are referred to in a comparison with the results of the present study

Hartmann (1879) found that an overpressure of 2–6 mm Hg (3–8 cm H_2O) in the nose gave passage through the normal Et during deglutition.

Zöllner (1942) made an investigation of the resistance of a normal Et in 200 airmen and got passage at 5 cm H_2O overpressure in the rhinopharynx in 68 % at 10 cm H_2O in 75 % and at 15 cm H_2O in 82 % of the cases (Zöllner determined tubal passage optically by an ear drum microscope)

Perlman (1943) made similar tests and got passage between 0–6 mm Hg (0–8 cm H_2O) overpressure in the nose in 10 cases of unobstructed tubes by inflation through the nose In 3 cases with tubal obstruction the required pressures were 30–50 mm Hg (40–68 cm H_2O)

Using Zöllner s method for application of pressure in the nose and recording tubal passage by determination of changes of the ear drum impedance Thomsen (1957) got passage in 83 % of the normal cases up to 10 cm H_2O overpressure in the nose.

Using Toynbee s manoeuvre which does not give a clearly defined pressure change in the rhinopharynx Zöllner described an investigation of 200 ears (1942) in which he got positive passage in 70 5 % of the cases.

In a series of normal ears Thomsen (1958) found that 72 % had positive Toynbee s manoeuvre i e showed passage through the tube

PRESSURE VARIATION IN THE MIDDLE EAR

For evaluation of the Et function studies based on pressure changes in the middle ear are far more interesting from a physiological point of view

Von Gyergyay (1932) made experiments on perforated ear drum cases with Toynbee s manoeuvre and got an underpressure in the middle ear He also observed but did not discuss the fact that the patient equilibrated the under pressure by swallowing

Holborow (1962) made experiments on anesthesized dogs to show the effect of the tensor veli palatini muscle on the mechanism of the tubal opening. Pressure was applied in the middle ear after incision of the ear drum. The pos

sibility of the ear to equilibrate this pressure was estimated, first when the tendon to the tensor veli palatini muscle was intact and second, after it had been cut. When the muscle was made to contract the Et opened and the pressure applied in the middle ear could be equilibrated. This was impossible after cutting the tendon to the tensor veli palatini muscle.

Miller (1965) published a material of ears investigated by the same aspiration method as the present author (Flisberg, Ingelstedt and Örtegren 1963). Miller found that after incision of the drum normal ears could equilibrate an applied underpressure in the ear in 100 % whereas only 43 % of ears with chronic otitis media in his whole material could do this. As a measure of the resistance of the Et Miller used the *residual pressure remaining after equilibration of negative pressure applied in the ear.*

Van Dishoeck (1947) took the middle ear pressure as a measure of tubal resistance. He measured the intratympanic pressure by the pneumophon method (van Dishoeck 1937). On 400 healthy ears van Dishoeck found a middle ear pressure less than 10 cm H_2O in 93 % of the cases.

By measuring the impedance of the ear drum Thomsen (1957) determined the threshold pressure necessary in the rhinopharynx to get tubal passage. He found that 83 % of the persons (100 normal cases) had threshold pressures of 10 cm water or less. Thomsen also determined the capacity of the tube to reduce the overpressure produced in the middle ear by deglutition. In 73 % the cases could completely equilibrate the overpressure.

The author s methods

EQUIPMENT AND BASIC METHODS

PRESSURE MEASUREMENTS

Ear

For pressure measuring in the ear a pressure transducer (electromanometer EMT 490 B Elema Schönander AB Stockholm) was used pressure range 0–30 mm Hg

The transformed pressure changes were amplified and recorded on a direct ink writing apparatus (Mingograph 24 B—Elema Schönander AB Stockholm) or on a Visicorder (model 906 S Honeywell)

The transducer was connected to the bony part of the external ear canal by a short nylon catheter (inner diameter 2 mm) which passed through an inflatable rubber cuff that closed the ear canal airtightly The cuff was firmly lodged in the bony part of the ear canal to preclude all blurring due to movement disturbances. The tightness of the system was checked by a manometer and endured all experimental conditions. The system was provided with a three-way stop-cock. A block diagram of the equipment is given in fig. 1

The transducer including catheter and cuff system was analysed for frequency response in model experiments. The frequency response of known sine wave pressures appears in fig. 2.

For absolute calibration an ordinary water manometer was used. The sensitivity of the transducer was adjusted so that a pressure change of 0–10 mm Hg gave a recorded linear deflection of 0–30 mm on the Mingograph. The same linear deflection on the Visicorder was 85 mm.

Nose

For pressure measuring in the nose a pressure transducer (electromanometer EMT 490 A Elema Schönander AB Stockholm) with a pressure range of 0–300 mm Hg was used. The pressure transducer was airtightly connected to the nostril by a catheter running through a nosepiece The same recording system as in pressure measuring in the ear was used.

The transducer with catheter was analysed for frequency response in model experiments. The frequency response of sine wave pressure variations appears in fig 2

For absolute calibration an ordinary water manometer was used. The sensitivity was adjusted so that 0–10 mm Hg gave a recorded linear deflection of 0–30 mm on the Mingograph and 75 mm on the Visicorder

Pressure changes in the ear or the nose were obtained by a device providing positive or negative square pressure waves according to Ingelstedt and Örtegren (1963) (see fig 3)

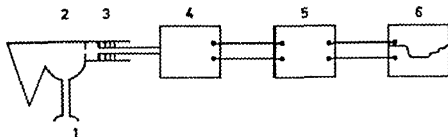


Fig. 1 Block diagram of equipment used in pressure measurements in the ear 1 Et and epipharynx 2. Air filled ear space 3. Rubber cuff 4. Pressure transducer 5. Amplifier 6 Recorder

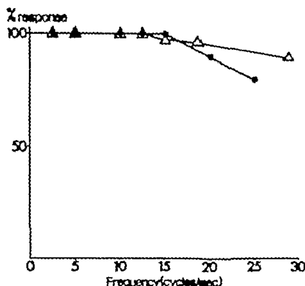


Fig. Frequency response curves for pressure measurements in ea and nose

△—△ Manometer system for recording pressure variation in the ear
●—● Manometer system for recording pressure variation in the nose.

FLOW MEASUREMENTS

For the investigation a flow rate meter device consisting of a differential pressure transducer with resistors amplifier and recording unit was used. Block diagram of the equipment is given in fig 3.

The differential pressure transducer had a working pressure range of ± 50 mm water level (pneumomanometer EMT 572 Elema Schönander AB Stockholm)

Different resistors could be connected to the differential pressure transducer by identical catheters which had the same damping effect. This was measured by giving sine pressure waves to both catheters simultaneously The membrane

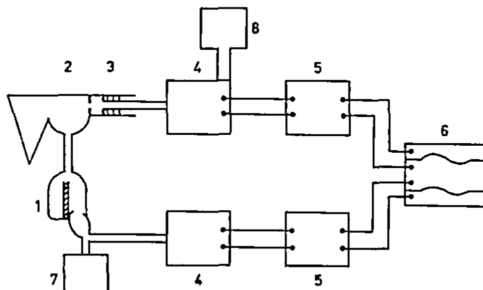


Fig. 3. Block diagram of equipment used in combined pressure and air flow measurements 1 Et, epipharynx and nose 2 Air filled ear space 3. Rubber cuff 4 Pressure transducer 5. Amplifier 6. Recorder 7 Equipment for giving square pressure waves in the nose 8. Equipment for giving under and overpressures in the ear

of the differential pressure transducer should then not move and cause any electrical signals

As resistors in the flow meter device could be used a Fleisch pneumotachograph nr 2040 as well as glass capillaries of different calibres and lengths coupled parallelly between two collecting units of glass

Three different resistor systems with 5 glass capillaries in each were devised. The different resistors were called

I. (length of capillaries 120 mm inner diameter 0 8 mm)
II (length of capillaries 140 mm, inner diameter 1.0 mm)
III (length of capillaries 50 mm inner diameter 1 5 mm)
IV (pneumotachograph nr 2040)

The pressure variations were amplified and recorded on a Visicorder (model 906 S Honeywell)

Calibration procedure

The flow meter device was calibrated with known constant air flows. Constant air flows were produced from gas tight glass syringes driven by an infusion device with a synchronous motor and different switches and by a rotameter (predictability flow meter FN 1044 B) In the case of the glass syringes absolute calibration was performed by filling the syringes with water and producing

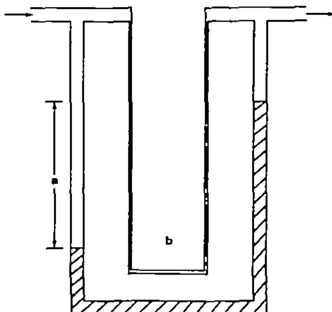


Fig. 4. Sketch of water differential manometer with resistor used at calibration procedures.
a. Distance between water levels during constant air flow through the manometer device
b. Exchangeable resistor

different flows between 2.4 and 75 ml/min. by using different speeds on the infusion device. The water volumes obtained after a fixed time could then be determined. For air flows from 75 ml/min. up to 850 ml/min. the rotameter was used. Absolute calibration of the air flows from the rotameter was made by water displacement.

The known constant air flows passed through a differential water manometer (see fig 4) It was possible to vary the sensitivity of the water manometer by using three different resistors. An example of a calibration curve for this manometer is given in fig 5.

As a matter of routine the water differential manometer was used as a basis for the absolute calibration of the flow meter device. The calibration was carried out for every investigation with the catheter system connected to the flow meter device. This was effected by placing the cuff airtightly in an artificial ear canal.

Resistor I was calibrated with known air flows and used up to an air flow of 55 ml/min. Resistor II was used up to 150 ml/min., resistor III up to 450 ml/min and resistor IV i. e. the pneumotachograph, calibrated for use up to 850 ml/min. An example of calibration curve for the flow meter device equipped with resistor II has been given in fig. 6.

Frequency response analysis of the entire recording system (catheter and flow meter device equipped with the different resistors) was performed. This was made on model experiments where cuff and catheter were lodged in an

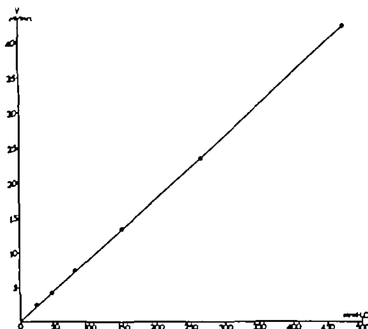


Fig. 5. Calibration curve for the water differential manometer in fig. 4 with constant known air flows. Resistor giving highest resistance was used.

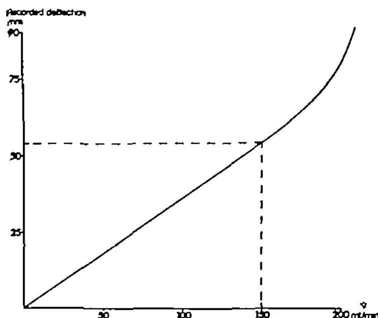


Fig. 6. Calibration curve for the flow meter device equipped with resistor II (see text) With this resistor the flow meter device was used up to 150 ml/min, which means a recorded maximal deflection of 55 mm on the scale of the recorder

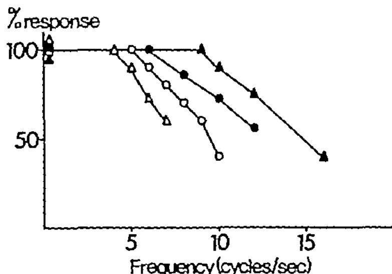


Fig. 7 Frequency response curves for the flow meter device equipped with the different resistors

Resistor I Δ—Δ Resistor III ●—●
II ○—○ IV ▲—▲

artificial ear canal. The given air flows were shaped as sine waves. The frequency response was calculated from the integrated curve. The frequency response curves are given in fig 7. The recording system must be sensitive enough. For this reason the system used was compared with another system where the frequency response was adequate up to 15 cycles/sec. This was performed on model as well as on patient experiments. The investigations showed that the different resistors provided adequate reproduction of all air flow rates obtained.

The frequency analysis was completed by an investigation with volumes added to the system in an effort to mimic the damping effect of different air cell systems. With added volumes of 5 and 10 ml no difference was given in the frequency representation.

The sensitivity of the flow meter device was so adjusted that maximum recording on the amplifier gave a recorded deflection of 65 mm on the scale of the Visicorder.

Integrator unit

The air flow could be integrated, whereby the total air volume passing through the Et was determined.

For the integrating circuit absolute calibration was made by determining the slope of the recorded integrated signals during known constant air flows.

Known air volumes produced by gas tight syringes (volumes 50 250 1000 5000 microliters) were further made to pass through the flow meter device. Calibration of this kind was performed in connection with every investigation

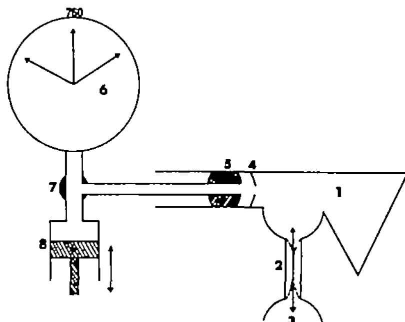


Fig. 8 Ear manometry Aspiration or deflation methods. 1 Air-filled ear space 2 Et; 3. Epipharynx 4. Ear drum, 5. Rubber cuff 6. Manometer 7 3-way stopcock, 8. Syringe (for producing desired pressures in the system)

EXAMINATION PROCEDURES

EVALUATION OF THE EUSTACHIAN TUBE FUNCTION BY PRESSURE MEASURING IN THE EAR (EAR MANOMETRY")

The method implies that pressure changes induced by deglutition in the closed ear manometer system is taken as an expression of the ventilatory ability of the Et. A pre-requisite for using the method was free air passage between the ear canal and the middle ear i. e a perforation in the ear drum should already exist or such a perforation had to be made by incision.

If a closed manometer system was airtightly connected to the external ear canal (fig 8) an applied under or overpressure in the system would remain unchanged for a short length of time till the Et opened, for example by swal lowing Pressure variation in the closed ear-manometer system could be produced by the investigator The degree of pressure change as well as changes occurring as a result of air passage through the Et were recorded.

EVALUATION OF AIR FLOW DIRECTION

At the opening of the Et air passes through the tube if there exists a pressure difference between the two ends of the Et. The direction of the air flow is con trolled by the pressures in the middle ear and the epipharynx.

For measuring of air flow direction the same equipment as that for pressure

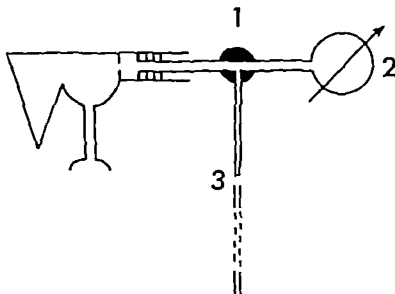


Fig. 9. Principle of measuring air flow direction by using open ear manometry 1 3-way stopcock, 2. Manometer 3. Catheter of variable length.

measurement in the ear was used, but the system could also be kept open ("open ear manometry") according to fig. 9. The length of the catheter used during measurement with open system was variable.

The pressure difference across the Et at measuring with closed system was performed by applying pressure in the middle ear and by swallowing with the nose closed (Toynbee's manoeuvre) By investigations with open system the pressure difference was performed only by Toynbee's manoeuvre.

EVALUATION OF THE EUSTACHIAN TUBE FUNCTION BY COMBINED PRESSURE AND AIR FLOW MEASUREMENTS

The purpose was to study the resistance to air flow offered by the Et during different conditions by using the methods and principles currently employed in respiratory physiology

The air flow ($\dot{V}$) through and the pressure differene (Δp) over the part of the airway that will be estimated are determined. The air flow resistance (R) is then $= \frac{\Delta p}{\dot{V}}$ (DuBois 1962 Comroe 1964)

It is possible to measure the pressure difference over and the air flow through the Et simultaneously and in this way to calculate the resistance according to the formula given above (Flisberg 1966)

The middle ear was connected airtightly to the described flow meter device

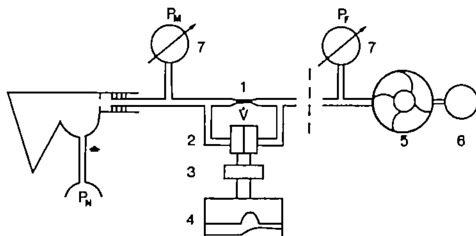


Fig. 10. Principle of air flow measurements. 1 Resistor in the flow meter device 2. Differential pressure transducer 3. Amplifier 4. Recorder 5. Electric fan 6. Autotransformer 7 Manometer P_F = pressure generated by an electric fan P_M = pressure in the middle ear P_N = pressure in the nose.

by means of a nylon catheter (inner diameter 2 mm) running through an inflatable cuff placed in the bony part of the external ear canal. The other side of the flow meter was open to the atmosphere or could be connected to an electric fan (fig 10) By the fan desired pressures could be applied in the ear (Different pressures in the nose were given as square pressure waves—see p 31) When an air flow passed through the Et in one direction or the other it also passed through the flow meter device and caused a pressure difference over its resistor This pressure difference was measured and recorded.

The errors arising from recording and calculating the air flows were analyzed (see statistical note) With few exceptions the error was less than ±20 %

The errors in calculating the pressure differences were always less than ±5 %

Depending on the construction of the integrating circuit there was an error in the integrated curve which varied with the time constant. By always using 20 sec. as time constant the error was less than 1 5 % during investigations where the measuring did not exceed 0 5 sec. At 1 sec the error had increased to 2 5 %

The pressure difference (Δp) over the Et could be determined by simultaneous measuring of the pressure in the ear and in the nose.

According to fig 10 $\Delta p = P_N - P_M$ during application of overpressure in the nose. At testing with application of underpressures in the nose $\Delta p = P_M - P_N$

At investigation with application of under or overpressures in the ear manometer system $\Delta p = P_F - P_M - P_N$ In general the pressure change of P_M at air passage through the tube was here so small that it could be neglected in relation to P_F As the nose was open P_N was the same as the pressure in the atmosphere and could be stated as zero Thus in these testings $\Delta p = P_F$

The difference between P_F and P_M at air passage through the Et was the same as the measured pressure difference of the differential pressure manometer Because of the magnitude of P_F and P_M compared to the pressure change of P_M at air passage through the Et it was convenient to measure this difference by a differential pressure manometer

The ideal pressure measuring in the middle ear should have been performed in the middle ear as closely as possible to the aural part of the Et. To be able to carry out different investigations during identical circumstances the rubber cuff equipment was used and the pressure was measured outside the ear The pressure drop which must then appear over the cuff with the catheter was determined in model experiments. The rubber cuff with the catheter was applied in an artificial ear canal and different air flows were made to pass through it. The pressure drop over the catheter at an air flow of 14 ml/sec. was 13.6 mm H_2O at an air flow of 6 5 ml/sec. 6 mm H_2O and at air flows up to 2 5 ml/sec. less than 2 mm H_2O

At air flows through the resistor in the flow meter device a certain amount of counterpressure must arise. This counterpressure was determined for the calibrated maximal air flows used on each resistor For resistor I the counterpressure was 4.7 mm H_2O for resistor II 4 0 mm H_2O for resistor III 2.0 mm H_2O and for resistor IV 1 5 mm H_2O

The total counterpressure was small and did not exceed 15 mm H_2O for air flows less than 14 ml/sec. At general recorded air flows the counterpressure seldom exceeded 6 mm H_2O

Calculation procedures at air flow measurements

Pressure changes, air flows and integrated air flow signals were recorded simultaneously on the Visicorder

The air flow at a certain point was determined by measuring the height of the deflection of the air flow curve at this point. This value was then entered on the calibration curve for the resistor used.

At determination of the air volume passing through the Et the height of the integrated curve was measured. The height was an expression of the air volume that had passed up to the measuring time point. Every recorded mm then meant a fixed volume which was different for every resistor in the flow meter device. Thus every mm recorded deflection on the integrated curve indicated for resistor I 7 microliters for resistor II 17 microliters for resistor III 100 microliters for resistor IV 167 microliters.

The air flow resistance offered by the Et was expressed in cm H_2O per ml/sec.

STATISTICAL NOTE

(In collaboration with F K. Mats Lärstad, Department of Statistics University of Lund)

The magnitude of the error of measurement was estimated by taking into account the linear dependence between the three variables x, y and z, where x is the calibrated constant

air flow y the distance between water levels on the differential water manometer and x the recorded deflection. It was only possible to make observations of the pairs (x, y) and $(y\ x)$ of the variables where the value of the first variable in the pairs was chosen in advance. The regression line was computed for the two pairs by means of the method of least squares and thus the two residual variances were estimated from the formulas:

$$s_y^2 = \frac{(n-1)\, s_y^2}{n-2}\left(1 - r_y^2\right) \text{ and } s_{x \cdot y}^2 = \frac{(n-1)\, s_x^2}{n-2}\left(1 - r_{xy}^2\right)$$

Finally an estimate of the residual variance of x in its dependence of both y and x was arrived at by means of the formula

$$s_{(y,x)}^2 = b^2{}_y\ s_y^2 + s_{x \cdot y}^2$$

(This formula is derived from statistical textbooks i.e. Rao C Radhakrishna Linear Statistical Inference and Its Applications Chapt. 4 New York 1965.)

The assumptions necessary for making this formula valid are independence between the errors of x, y and z, and independence between the error and the value of the variable. The errors must be normally distributed.

To relate the errors of measurement in x to a simple form, 3σ-limits were computed and divided with a value in the middle of th range for each resistor in the flow meter device.

The 3σ-error in per cent for each resistor at mid value of x then was: I. ± 14 % II. ± 9 % III ± 17 % IV ± 12 %.

Other Eustachian tube function methods used

POLITZER S METHOD

By increasing the pressure in the nose with a Politzer s bag while the patient swallows it is possible to force air into the middle ear In fig. 11 the lower curve of the Politzer procedure illustrates the pressure variation in the nose and the upper curve the pressure variation in the ear

GRADED INFLATION

A pressure was applied in the rhinopharynx as a square pressure wave simul taneously with the patient s swallowing Air passage through the Et was recorded with the same system as that used at pressure measurement in the

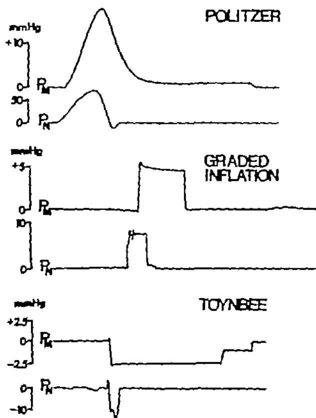


Fig. 1 Examples of pressure measuring in nose and ear at positive testings with Politzer method, graded inflation and Toynbee s manoeuvre.

ear The lowest pressure necessary for tubal passage was determined and a quantitative value of the ability to get tubal passage was given In fig 11 at the investigation of graded inflation the pressure in the nose was changed by a square pressure wave (lower curve) while the upper curve shows how the pressure changed in the middle ear

TOYNBEE S MANOEUVRE

By swallowing with the nose closed the pressure in the rhinopharynx is changed. The tube opens during the act of swallowing and a pressure variation in the ear is induced. An example of pressure changes in the nose and ear is seen in fig. 11

Experimental procedures

Identical experimental conditions were preserved in the different investigations. The subject sat in an examination chair with a headrest. In some cases with patulous tubes the examination was also undertaken with the patient in a recumbent position. Swallowing was induced by letting the subject drink water. The investigations were made as short as possible to minimize thermal influence.

Between the different testing moments there were pauses of $^1/_2$–1 min. The underpressures were only applied during very short periods of time except during loading tests.

The following investigations were made

EAR MANOMETRY

Air passage through the Et was induced by the following methods

Politzer's method.

Application of graded positive pressures in the rhinopharynx (t... The pressures were +5 +10 +15, +20 +25 +30 and ... +40 cm H_2O

Toynbee's manoeuvre.

Application of negative pressures in the middle ear (aspir... testing of the capacity for equilibrating the pressure at swa... sures were −2 −5, −10 −20 and −30 mm Hg

Application of positive pressures in the middle ear (defl... testing of the capacity for equilibrating the pressure at sw... sures were +2, +5, +10 +20 and +30 mm Hg.

By *studying the negative dip phenomenon* close as well as ... was performed. Ordinary deglutition and Toynbee's man... induce the phenomenon.

EVALUATION OF AIR FLOW DIRECTION

Toynbee's manoeuvre was used to produce pressure differences across the Et. During measuring with a closed system Toynbee's manoeuvre was combined with pressure application in the middle ear

EVALUATION OF THE EUSTACHIAN TUBE FUNCTION BY COMBINED PRESSURE AND AIR FLOW MEASUREMENTS

Air passage through the Et was induced by the following methods

Politzer's method.

Application of graded positive pressures in the rhinopharynx (graded inflation) The pressures were kept so that the pressure differences across the Et were +10 +20 +30 and in some cases +40 cm H_2O

Application of graded negative pressures in the rhinopharynx. The pressure differences across the Et were −10 −20 −30 and in some cases −40 cm H_2O

Application of negative pressures in the middle ear (aspiration method) and testing of the capacity for equilibrating the pressure at swallowing The pressures were −10 −20 −30 and in some cases −40 cm H_2O

Application of positive pressures in the middle ear (deflation method) and testing of the capacity for equilibrating the pressure at swallowing The pressures were +10 +20 +30 and in some cases +40 cm H_2O

The pressures in the ear during testing with the aspiration and deflation methods in air flow measurements were obtained by connecting a fan with that part of the flow meter device that faced the atmosphere.

Application of a constant underpressure in the middle ear

An underpressure of −30 cm H_2O was continually applied in the middle ear by a fan connected with the flow meter device as described above. The pressure was continually kept up to 25 minutes. At intervals of 5 minutes the air flow through the Et during swallowing was recorded.

Pressure measuring in the ear was performed on 102 patients with the diagnosis of chronic otitis media. All had central perforation of the ear drum and myringoplastic operations were considered. The investigation was performed at least twice on every patient on different occasions (intervals more than two weeks) (Tables I and II) In this material 6 ears with patulous tubes were found) (Table VII)

Attempts were made to divide the material according to the duration of the disease. There were great difficulties in obtaining reliable information about how long the patients had had perforations of their ear drums. The number of patients who could yield reliable information was so small that no conclusions could be drawn. Knowledge about the duration of the periods of discharge should also have been valuable. However it was found that also in this respect the patient's information was so unreliable that a valid estimation of the duration was not even attempted.

Pressure measuring in the ear was also performed on a material of 36 patients with healthy ears (Tables III and IV) In these ears incision of the ear drum had to be made before the testing. In these cases the investigations could for natural reasons be performed only once The investigation was made on healthy volunteers and in patients with tinnitus or hearing impairment of unknown origin. The length of the incision was at least 2–3 mm and the perforation was made in such a way that it remained open.

There must be no history of otitis media or serous otitis The drum should be normal and freely movable. In all these cases the perforation after incision healed up without complications.

Tables I and II. *Cases of chronic otitis media investigated by pressure measuring in the ear*
(Six cases of patulous tube are given in Table VII.)

Age distribution

Years	Number of ears
7–20	22
21–40	32
> 40	42
Total number	96

Sex distribution

Men	Women	Total number of ears
5	45	96

Tables III and IV *Cases of healthy ears investigated by pressure measuring in the ear*

Age distribution

Years	Number of ears
18–20	4
21–40	16
> 40	6
Total number	36

Sex distribution

Men	Women	Total number of ears
20	16	36

Tables V and VI. *Cases of chronic otitis media investigated by combined pressure and air flow measurements*

Age distribution

Years	Number of ears
12–20	8
21–40	20
> 40	13
Total number	4

Sex distribution

Men	Women	Total number of ears
1	20	41

Table VII. *Patulous tube cases*
Pressure measuring in the ear

Number of ears	Age in years	Men	Women
6	11 3, 20 25, 33, 39	1	5

Table VIII. *Patulous tube cases*

Combined pressure and air flow measurements

	Number of ears	Age in years	Men	Women
Cases with chronic otitis media		27 43		–
Cases with incision of the drum	5	17 22, 44, 44, 56	3	2
Total	7	17–56	5	

Combined pressure and air flow measurements were made on a series of 41 patients with chronic otitis media and central perforations of the ear drums (Tables V and VI)

Five patients with intact ear drums hade discomfort from patulous tube In these cases incision of the ear drum was performed and investigation by com bined air flow and pressure measurements were made The perforations of the ear drums were about 3-4 mm long As in the case of the healthy subjects, they were made so as to remain open. The reason was that the air flow resistance must not increase All incised ear drums healed up without complica tions (Table VIII)

In ears with chronic otitis media the perforations of the ear drum were so large that increased air flow resistance could be disregarded.

Investigations were made on suitable ears of the present material by measuring the air flow direction and by studying the negative dip phenomenon.

All ears with chronic otitis media had been dry and without discharge for at least one month before every examination The patients had no complaints from the respiratory tract and no nasal obstruction or discharge from the nose. In addition to ear examination inspection of nose epipharynx and larynx were made in all cases. This examination did not reveal anything abnormal.

Results and comments

EAR MANOMETRY

ASPIRATION—DEFLATION

A normal ear should be able to equilibrate an underpressure applied in the ear From the results it also appears (Table IX) that all normal ears succeeded in establishing such an equilibration which is in accordance with Miller's investigation of 1965

In ears with chronic otitis media on the other hand, a similar equilibration took place only in 42 % (Table X) Thus there was a great difference between normal ears and ears with chronic otitis media as regards their capacity for equilibrating an underpressure.

A comparison between the author's material and Miller's (1965) consisting of 180 ears with chronic otitis media and 17 normal ears gives similar results. Thus Miller reported that among his 180 ears with chronic otitis media 79

Table IX. *Positive tubal function tests in normal ears after incision of the drum*
(Positive aspiration and deflation testings = obtained equilibration of applied pressures in middle ear
Positive graded inflation Politzer and Toynbee testings = obtained passage through the Et.)

Number of ears	Aspiration	Deflation	Graded inflation		Politzer	Toynbee's manoeuvre
			0– cm H_2O	0–25 cm H_2O		
20 men	20	20	20	20	20	7
16 women	6	16	16	6	6	13
Total 36	36	36	36	36	36	30

Table X. *Positive tubal function tests in ears with chronic otitis media*
(Positive testings see Table IX.)

Number of ears	Aspiration	Deflation	Graded inflation		Politzer	Toynbee manoeuvre
			0– 0 cm H_2O	0–25 cm H_2O		
51 men	9	29	2	37	51	17
45 women		27	22	33	44	3
Total 96	40	56	43	70	95	30

The results of each examinee at this type of measurements are not given but may be obtained from the University Library Lund or from the author

(43 %) had a relatively good Et function and could equilibrate an underpressure applied in the middle ear

Miller reported 54 ears with normal tympanic mucosa. These ears should be more comparable with the author's material of ears with chronic otitis media. Among the ears in Miller's material with a normal tympanic mucosa 32 cases (60 %) could equilibrate an underpressure, i. e. a higher value than the present author's.

At investigation of the ears by the methods based on application of under or overpressures in the ear (aspiration and deflation methods) the following curve types could be distinguished

a) Capacity for equilibrating under and overpressures applied in the middle ear directly to o-level, (fig 12)
(o-level = surrounding atmospheric pressure during the investigation with range of ± mm Hg.)
b) Capacity for equilibrating under and overpressures applied in the middle ear stepwise to o-level (fig. 13)
c) Equilibration only for applied negative and positive pressures exceeding ± 20 mm Hg.
d) Equilibration only for applied positive pressure.
e) No capacity for equilibrating pressures.
f) Spontaneous emptying through the Et of applied positive pressure in the middle ear without deglutition.

The distribution of types a–e in normal ears and ears with chronic otitis media appears from tables XI and XII.

Table XI. *Type of pressure equilibration in normal ears*

	Type of equilibration		
	Directly to o level	Stepwise to o level	Number of ears
Aspiration	8	8	36
Deflation	20	6	36

Table XII. *Type of pressure equilibration in ears with chronic otitis media*

	Type of equilibration		Only for	equilibration	Number
	Directly to level	Stepwise to o level	pressure differences > ±20 mm Hg		of ears
Aspiration		29		56	96
Deflation	3	32		40	96

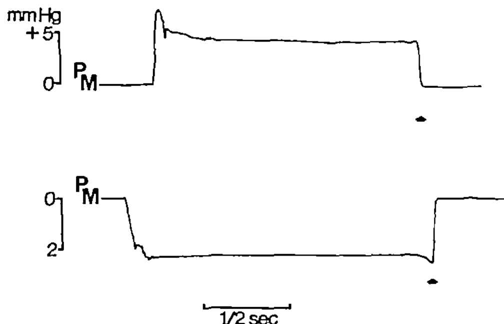


Fig. 12. Recordings in a normal case with ability to equilibrate applied over and underpressures in the ear directly to o-level. Filled arrow indicates deglutition.

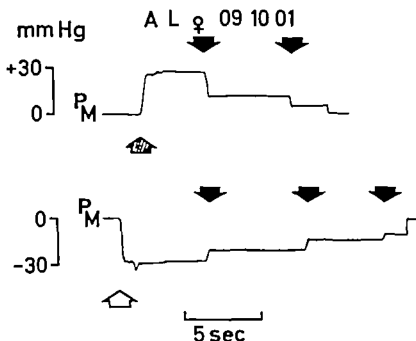


Fig 13. Recordings in a case of chronic otitis media with ability to equilibrate applied over and underpressures stepwise to o-level. Filled arrow – deglutition, Shaded arrow – application of positive pressure in the ear· Hollow arrow – application of negative pressure in the ear

The author thus found that pressure equilibration could take place in two different ways namely directly to o-level and stepwise to o-level (figs. 12 and 13) Among the normal ears the equilibration of underpressures took place directly in 50 % of the cases and stepwise to o-level in 50 % The ears with chronic otitis media which could equilibrate an underpressure did so stepwise in 75 % and directly to o-level in 25 % (Tables XI and XII) At present both types of equilibrations are regarded as normal. Equilibration directly to o-level must imply a very good ventilatory function of the Et whereas the stepwise equilibration may indicate a slightly smaller ventilatory capacity of the Et.

Some ears (Table XII) could only equilibrate high over and underpressures. Miller (1965) reported several cases of this type in his material. These ears are examples of a kind of reduced capacity for equilibrating In these cases the Et function is dependent on a further factor beyond the normal active muscular opening mechanism. A high pressure difference must exist across the Et to bring about the tubal opening and pressure equilibration.

In some cases spontaneous emptying of air through the Et at application of overpressure in the middle ear takes place at relatively small pressure—below +15 mm Hg. This may mean a tendency towards the condition of patulous tube. This small emptying pressure in certain cases was already observed by Hartmann (1879) At a sufficiently high positive pressure in the middle ear spontaneous emptying of air via the Et normally takes place In the present investigation this emptying was found to take place between +15 and +40 mm Hg (20–54 cm H_2O) which is in agreement with the values of earlier investigators (Hartmann 1879 Armstrong and Heim 1937) Spontaneous equilibration of underpressure applied in the middle ear without deglutition was only noticed in ears with patulous tubes.

INTRATYMPANIC RESIDUAL PRESSURE

Those ears in the author's material which could equilibrate an underpressure generally did so according to the all or none law With few exceptions the equilibration took place to the o-level (Table XIII) A residual pressure (±2 mm Hg = 2 7 cm H_2O) could then be found. This was considered to be normal and was noticed in normal ears as well as in cases with chronic otitis media.

Table XIII *Intratympanic residual pressures after pressure equilibration in ears with chronic otitis media*

	< mm Hg	2–5 mm Hg	> 5 mm Hg	Number of ears
Aspiration	35	4		40
Deflation	48	1	7	56

Among the 79 ears that could equilibrate underpressures however Miller (1965) found 55 ears (70 %) with residual intratympanic underpressure of from 0 to −5 cm H_2O 24 ears (30 %) had Et thresholds greater than −5 cm H_2O (average threshold of −14.4 cm H_2O) Miller stated that a certain pressure dif ference across the Et was necessary for equilibration. For this reason Miller regarded the residual pressure after equilibration as an expression of the func tion of the Et.

The selection of material may explain this difference in the presence of residual pressures in Miller s (1965) and in the author s material. Thus Miller also examined ears with changes of the mucous membranes in the middle ear Such ears were excluded from the present material. It is possible that the mucous membrane factor including swollen mucous membrane and increased secretion was of some importance in Miller s investigation.

PATENCY OF THE EUSTACHIAN TUBE TO INFLATION

Tables IX and X were obtained by pooling the results of the tubal function investigations performed with the different methods based on ear manometry

43 ears (45 %) with chronic otitis media had tubal passage with the graded inflation method at a threshold pressure below 10 cm H_2O At application of an overpressure of up to 25 cm H_2O in the nose 70 ears (73 %) had positive inflation testing

By Politzer s inflation method, passage was obtained in 95 cases i e. almost in 100 % With this method it is however impossible to determine exactly at what pressure in the nose tubal passage is reached (see fig 11)

TOYNBEE S MANOEUVRE

At Toynbee s manoeuvre the author found passage through the Et in 83 % of the normal cases (Table IX) This number is a little higher than that of earlier investigators (Zöllner 1942 Thomsen 1958) This may be due to the fact that unlike Zöllner and Thomsen the author made the investigation after incision of the ear drum. The drum however probably damps small pressure changes in the middle ear The negative Toynbee tests obtained may be due to an unsatisfactory recording procedure or naturally to a real lack of tubal passage. In ears with chronic otitis media passage with Toynbee s manoeuvre was obtained only in 31 % of the ears (Table X) It is impossible to say how many and which ears with a normal Et function are "lost among the ears with chronic otitis media as assessed by the use of this testing procedure.

COMPARISON OF THE DIFFERENT METHODS

In the analysis of the different tubal function methods it is important to compare the aspiration method and the different inflation methods In view of the

Table XIV *Comparison between aspiration and inflation methods. Pressure threshold in the nose < 10 cm H_2O*

Inflation 0– 0 cm H_2O	Aspiration +	Aspiration –	
+	37	6	43
–	3	50	53
	40	56	96

These ears had a positive inflation test at 15 cm H_2O

\+ air passage through the Et.

– no air passage through the Et.

Table XV *Comparison between aspiration and inflation methods. Pressure threshold in the nose < 15 cm H_2O*

Inflation 0– 5 cm H_2O	Aspiration +	Aspiration –	
+	40	30	70
–	0	26	26
	40	56	96

\+ air passage through the Et.

– no air passage through the Et.

author's opinion on the normal tubal function it seems logical to take the aspiration method as a standard and compare it with the other methods.

Taking ears with chronic otitis media which could equilibrate an underpressure in the ear as a basis, it is of interest to see at what overpressure applied in the nose these very ears obtained tubal passage. In the author's material it was proved that if 10 cm H_2O was chosen as an upper limit of overpressure in the nose there was a very good conformity between positive aspiration testing and positive inflation testing (Table XIV) If on the other hand the upper limit

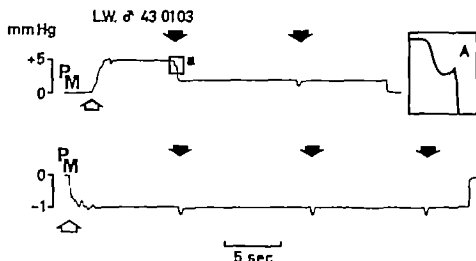


Fig. 4. A case of common cold illustrating negative pressure spikes during ordinary deglutition at close ear manometry. Detail of curve magnified to the right. Filled arrow – deglutition. Shaded arrow – application of positive pressure in the ear. Hollow arrow – application of negative pressure in the ear

of inflation pressure was kept at +25 cm H_2O a poor conformity was obtained (Table XV). Such a poor conformity was also found on comparison between Politzer's method and a positive aspiration testing. Judging from this comparison between the aspiration and inflation methods there should thus be no objection to taking the upper limit for graded inflation to 10 cm H_2O overpressure in the nose as a clinical standard.

By repeating the investigations the reproducibility of the method could be assessed. With the aspiration method there was no difference between the investigations. With the method of graded inflation there was a very slight difference in the pressure necessary for getting tubal passage. When the cases were divided into different age groups no certain difference was observed between the groups at the various testings. No difference between the sexes was proved.

NEGATIVE DIP PHENOMENON

During investigations of patients with common colds Flisberg, Ingelstedt and Örtegren (1963) observed a phenomenon referred to above as the negative dip phenomenon. This was manifest as a negative pressure spike in the middle ear when the patient swallowed. In the present investigation the phenomenon was found also on several patients without any sign of infection. By using close as well as open ear manometry there were possibilities to study the presence of the phenomenon in certain cases during Toynbee's manoeuvre and ordinary deglutition with open nose. The findings are illustrated in figs. 14 and 15.

In fig. 14 (close ear manometry) it is shown how the tendency of locking

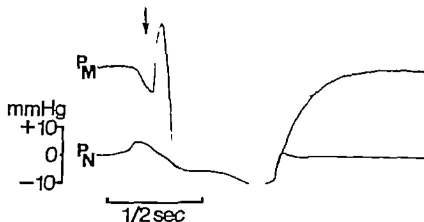


Fig. 15. A normal volunteer without infection showing negative dip phenomenon by performing Toynbee manoeuvre at open ear manometry The upper curve illustrates pressure changes in the ear The lower curve illustrates pressure changes in the nose Arrow indicates the negative dip.

in the Et was overcome by the pressure difference (+5 mm Hg) The negative pressure spike was broken and equilibration was produced. Negative dips without equilibrations were effected at positive as well as negative pressures in the middle ear

By using open ear manometry a negative dip appeared simultaneously with the positive phase of Toynbee's manoeuvre as illustrated in fig. 15

EVALUATION OF AIR FLOW DIRECTION

The pressures on both sides of the Et determine the direction of air flow at the tubal opening With different pressures in the middle ear during closed ear manometry the air flow direction was studied by performing Toynbee's manoeuvre The results are illustrated in fig 16

The pressure variations in the nose during Toynbee's manoeuvre were almost the same in the four examinations. From the figure it appears that

a) An applied moderate overpressure in the middle ear became negative
b) A high overpressure in the middle ear was not entirely equilibrated to ...
c) A moderate underpressure became still more negative The small p... pressure phase in the rhinopharynx that initiated Toynbee's manoeu... however a transient raise of pressure in the middle ear
d) With a large underpressure a small equilibration towards ze... obtained.

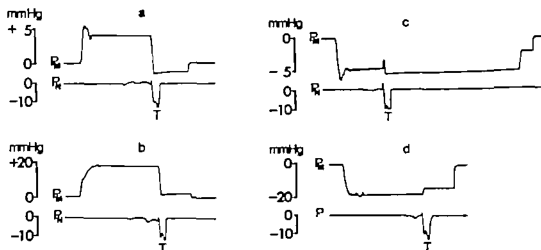


Fig. 16. Example of different air flow directions through the Et by performing Toynbee's manoeuvre in a normal volunteer After drum incision various pressures were applied in the middle ear See text. T = Toynbee's manoeuvre

At open ear manometry different air flow directions could be found by performing Toynbee's manoeuvre (fig 15) The negative spike was broken at the opening of the Et and air was forced into the middle ear as long as the pressure in the rhinopharynx was positive and thus exceeded the middle ear pressure At the second phase of Toynbee's manoeuvre when the pressure in the rhinopharynx became negative air was sucked out from the middle ear—the air flow had changed direction. If the Et closes during this period a negative pressure remains in the normal middle ear (compare fig 16 a and c)

COMBINED PRESSURE AND AIR FLOW MEASUREMENTS

At this type of measurements the ears were divided according to the Et function. This division was based on the results of pressure measuring in the ear Three groups were distinguished

- Group I cases with capacity for equilibrating underpressure applied in the ear (20 ears)
- Group II cases with no capacity for equilibrating underpressure applied in the ear (19 ears)
- Group III patulous tube cases (7 ears)

The measurements were repeated and the series with highest air flow values for every individual was selected. The air flows in the different testing manoeuvres are given in Tables XXV–XXIX (see Tables pp 80–82) The maximal

air flow at every pressure difference across the Et was calculated. Corresponding air flow resistance thus means minimum resistance. By mean is always meant the arithmetical mean.

The difference (d_i) between two measurements at different examinations of the same patient was used to estimate the variation. This calculation was made from measurements at graded inflation with 30 cm H_2O pressure difference across the Et. The error of the method will be included in this variation.

The coefficient of this variation $= \frac{\sqrt{\Sigma\ d^2/n}}{m}$ was then

Group I. 17 %
Group II 6 %
Group III [illegible] %
(calculation made in collaboration with F. K. Mats Lörstad)

There were fairly great differences in air flow values among the different individuals of group I and II obviously due to the fact that the investigations were made on ears with varying lesions in the middle ear and the Et.

At *graded inflation* group I had air flow resistance values ranging between 5 and 50 cm H_2O/ml/sec. (Tables XVI and XVII)

Table XVI. *Air flow resistances at graded inflation testings*

R cm H_2O/ml/sec.	h_1 = cm H_2O			Δp = 10 cm H_2O			Δp = 1 cm H_2O		
	Group			Group			Group		
	I	II	III	I	II	III	I	II	III
0–5	0		6		0	7	0		5
5–50	9	0	1	9			9	2	2
> 50		2	0	1	6	0		0	
Number of ears	10		7	10	6	7	20	2	7

In ears no passage could be recorded t 1 cm H_2O pressure difference.
In 6 ears no passage could be recorded t 10 cm H_2O pressure difference

Group I. cases with capacity for equilibrating underpressure applied in the ear
Group II. cases with no capacity for equilibrating underpressure applied in the ear
Group III patulous tube cases

Table XVII. *Mean air flow resistances at application of over pressure in the nose (graded inflation)* (Group I)

	R cm H_2O/ml/sec.			
	Δp cm H_2O			
	10	20	30	40
Mean air flow resistance	25.2	9.3	15.5	9.0
Standard deviation	± 3.0	±9.8	±8.3	±5.1

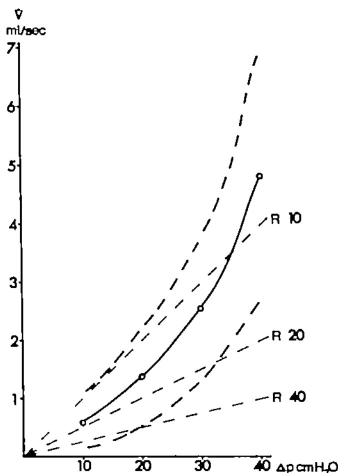


Fig. 17 Maximal air flows at varied pressure differences at graded inflation testing. Mean values of group I are given. (At 40 cm H_2O pressure difference across the Et 7 ears were tested.) Isoresistance lines showing resistances of 10 20 and 40 cm H_2O/ml/sec. are drawn

Δp	pressure difference across the Et
$\dot{V}$	maximal air flow through the Et
O——O	mean air flow
— — —	mean air flow ± X standard deviation
— — —	isoresistance lines

The mean air flows and air flow resistances are shown in figs. 17 and 18 (On calculating these diagrams one case was excluded because of extreme values. In this case the air flow resistance values ranged between 140 and 170 cm H_2O/ml/sec) From the diagrams it is evident that the air flow increases with increasing pressure difference across the Et and that the corresponding air flow resistance diminishes.

In group II sixteen ears were still inflatable with positive graded pressures. These tubes had air flow resistances exceeding 50 cm H_2O/ml/sec (see Table

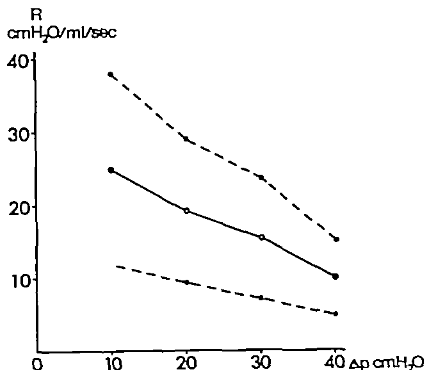


Fig. 8. Minimal air flow resistances and standard deviations at varied pressure differences at graded inflation testing. Mean values of ears in group I are given.

O—O mean air flow resistance
– – – mean air flow resistance ±1 x standard deviation

XVI and fig 19) From Table XVI are excluded 4 ears which were only inflat able at a minimum threshold of 40 cm H_2O These ears had the following air flow resistances at a pressure difference of 40 cm H_2O 40 63, 96 and 216 cm H_2O/ml/sec.

Politzer s method was the only successful one in the case of three patients in the series of chronic otitis media, where graded inflation up to 30 or 40 cm H_2O in the nose did not give tubal passage. The resistance values at testing these tubes were

52	cm H_2O/ml/sec	at Δp of	108	cm H_2O
60	„ „	„ „ „	130	„ „
236		„ „ „	118	„ „

The third group (7 ears group III) containing ears with chronic otitis media as well as ears with incision of the ear drum showed patulous tubes. Among these the air flow resistance values by inflation testings were all below 5–6 cm

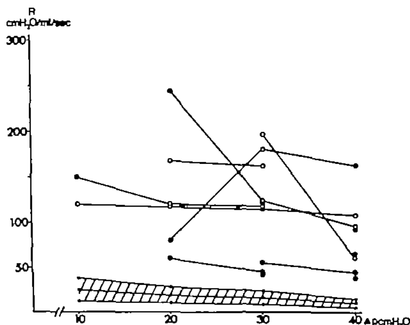


Fig. 19 Air flow resistances of group II tested with graded inflation.

● Testing performed only at one pressure difference across the Et.
○ Testing performed at several pressure differences across the Et.
(For comparison the minimal air flow resistances with standard deviations of group I tested with graded inflation are sketched – shaded area.)
(Primary air flow values of group II are given in Table XXVIII.)

H_2O/ml/sec. (Table XVI) Fig 20 shows the air flows at inflation and aspiration testings of group III at different pressure differences across the Et. Also at aspiration testing it appears from this figure that the resistances were low (below 7 5 cm H_2O/ml/sec.)

A great difference in air flow resistance between the groups at graded inflation testing could thus be demonstrated.

The mean values of air flows in group I at *aspiration testing* are illustrated in fig 21 This test was performed in 13 of the cases (Two cases with extreme values were excluded from the statistical analysis. One of these was the same as the one excluded at graded inflation The calculated air flow resistances in this case ranged between 66 and 120 cm H_2O/ml/sec. The other case had resistance values between 66 and 275 cm H_2O/ml/sec.)

From the isoresistance lines drawn in the diagram it appears that there may be a small tendency for the air flow resistance to increase with increasing pressure differences across the Et (compare fig 17) In Table XVIII the calculated mean resistance values at different pressure differences are given.

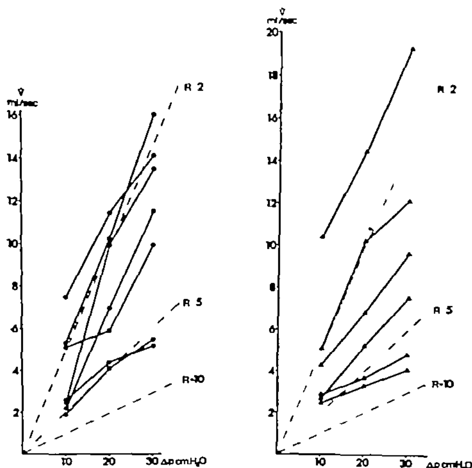


Fig. 20 Air flows in patulous tube cases. In the left diagram testing was performed with graded inflation in the nose (7 ears) In the right diagram testing was performed with applied underpressure in the ear (6 ears) In both diagrams the isoresistance lines showing resistances of 2 5 and cm H_2O/ml/sec. are drawn (— — —)

For pressure differences higher than 10 cm H_2O it was also found that the air flow resistances were higher at aspiration testing than at graded inflation testing at the same pressure difference (compare Tables XVII and XVIII)

Application of graded underpressure in the nose in 11 cases of group I gave mean values of air flow resistances as shown in Table XIX. In fig 22 the mean maximal air flows at different pressure differences are sketched together with calculated isoresistance lines. It is seen that there is a small tendency for the air flow resistance to increase with increasing pressure differences (In the statis tical analysis two ears with extreme values were excluded—the same ears as those excluded at aspiration testing In the remaining nine cases the testing was unsuccessful in three and not performed in six cases.)

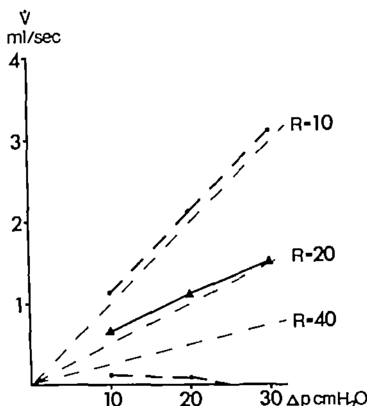


Fig 21 Mean air flows with standard deviations at aspiration testing of group I. Isoresistance lines showing resistances of 10 20 and 40 cm H_2O/ml/sec. are drawn.

▲—▲ mean air flow
● – ● mean air flow ± 1 x standard deviation
— — isoresistance lines

Table XVIII. *Mean air flow resistances at application of underpressure in the ear* (aspiration) (Group I)

	R cm H_2O/ml/sec.		
	Δp cm H_2O		
	10	20	30
Mean air flow resistance	25.2	31.9	38.9
Standard deviation	±16.3	±21	±26.2

Table XIX. *Mean air flow resistances at application of underpressure in the nose* (Group I)

	R cm H_2O/ml/sec.		
	Δp cm H_2O		
	10	20	30
Mean air flow resistance	25.6	40.7	53.8
Standard deviation	± 4.9	±17.4	±24.8

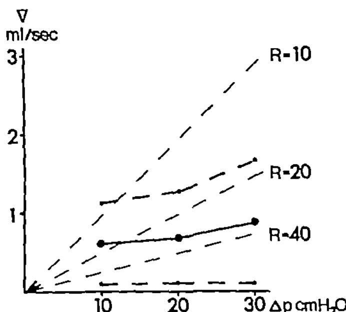


Fig. 22. Mean air flows with standard deviations at application of graded underpressure in the nose of group I. Isoresistance lines showing resistances of 1 20 and 40 cm H_2O/ml/sec. are drawn.

●——● mean air flow
● ● mean air flow ± 1 standard deviation
— — isoresistance lines

Table XX. *Air flow resistances at various pressure differences across the Et in two cases of chronic otitis media with good Et function*

	R cm H_2O/ml/sec.			Patient
	Δp cm H_2O			
	0	20	30	
Application of under pressure in the nose	5	49	90	H. H. ♂ 0 0707
	32	37	58	L. R. ♂ 400513
Application of over pressure in the ear	7 5	1	↓	H. H. ♂ 010707
	22	3 ↓	↓	L. R. ♂ 400513

At pressure differences of 20 and 30 H_2O a tendency towards continually open Et arose at application of positive pressures in the ear (indicated by the arrows)

At testing with *application of overpressures in the ear-flow-meter system (deflation method)* the air flow resistances were determined. The resistances were always below the corresponding values at application of graded underpressures in the nose although the air flow direction was the same in both testings. As an example the air flow resistance values are given for two ears with chronic otitis media and with capacity for equilibrating underpressures in the middle ear (Table XX)

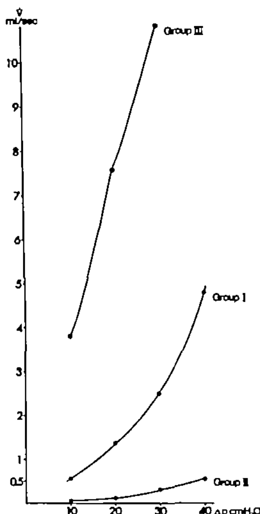


Fig. 3. Mean air flow curves from groups I, II, and III at graded inflation testings. (Primary air flow values are given in Tables XXV XXVIII and XXIX.) Extrapolation of curve from group I has been made—expressed by broken lines.

In respiratory physiology the airway resistance is determined at a fixed air flow rate On principle this can also be done at measurements of the resistance of the Et. However because of the very different air flow rates through the Et of different individuals it is very difficult to compare the individuals as well as the groups of the author s investigation In fig 23 the mean air flow curves at graded inflation testing of the three groups are drawn These curves may of course be discussed. Thus in group I the air flow at 40 cm H_2O pressure difference is only calculated from investigations of 7 ears In group II it was possible to obtain passage only in 2 tubes at 10 cm H_2O pressure difference in 6 at 20 cm H_2O pressure difference in 12 at 30 cm H_2O pressure difference and only in 9 ears was the investigation made at 40 cm H_2O pressure difference. From a statistical point of view even zero values should have been included. However this would have made a comparison impossible

Between the groups I and III a comparison at an air flow of 5 ml/sec. can be made after extrapolation of the curve of group I. The calculated resistance values were then

Group I 8.2 cm H_2O/ml/sec.
Group III 2.8 „ „

This apparently means that also in a comparison with this form of calculation the resistance values are lowest among the patulous tube cases.

Between the groups I and II a comparison can be made at an air flow of 0 5 ml/sec. after extrapolating the curve of group I. The calculated resistances were then

Group I 18 cm H_2O/ml/sec.
Group II 76 „ „

A great difference in resistance between the groups was thus also shown by this calculation procedure

TYPICAL CASES

In figs. 24–27 examples are given of combined pressure and air flow measuring during testing an ear with chronic otitis media and with an Et capable of equilibrating an underpressure. The maximal air flows and corresponding air flow resistances during the different testings appear from Table XXI.

From the case in figs. 24–27 the different testing values have been related to varied pressure differences across the Et in figs. 28 and 29. The diagram in fig 29 illustrates how the air flow resistance increased during aspiration testing and testing with graded underpressure in the nose while the resistances diminished at inflation and deflation testings. As comparison testing values from a patulous tube case are also given in fig. 29

In fig 30 a case of chronic otitis media with a poorly functioning Et tested with graded inflation is illustrated. The aspiration testing was negative. The pressure difference across the Et necessary to obtain tubal passage was 40 cm H_2O During pressure application in the nose a level of air flow through the Et appeared. This level remained as long as the pressure in the nose remained even after the end of the swallowing phase. From table XXII appears air flow values and corresponding air flow resistances at maximal flow as well as at level flow The air flow resistance value was lowest during the active phase of deglutition.

Testing a case of chronic otitis media with a poorly functioning Et by Politzer's method is illustrated in fig. 31 In this case tubal passage was obtained first at very high inflation pressure in the nose ($\Delta p = 118$ cm H_2O) The maximum air

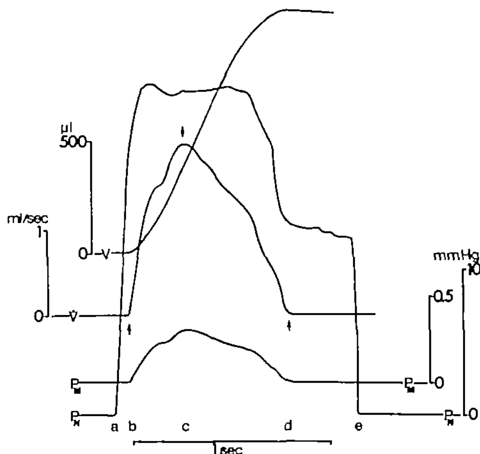


Fig 24 Combined pressure and air flow measuring in case of chronic otitis media tested with graded inflation at a pressure difference of 30 cm H_2O (22.0 mm Hg) across the Et.

a. pressure application in the nose b. Et opening, c. point of maximal air flow d. Et closure e ending of pressure application (the arrows correspond to the different letters) V – volume of air passing the Et V – air flow through the Et P_M – pressure in the middle ear P_N – pressure in the nose
(Owing to technical difficulties it proved too expensive to reproduce the original curves obtained by the Visicorder (Honeywell) The figures showing flow curves have been copied with Indian ink)

flow was 0 5 ml/sec. and the corresponding air flow resistance 236 cm H_2O/ml/sec which means a high resistance

During certain inflation procedures a level in the air flow curve was produced as illustrated in fig. 30 By testing patulous tube cases levels were regularly observed on the air flow curve at testing with graded inflation An example of this is given in fig. 32.

At a 20 cm pressure difference across the Et produced by graded inflation as

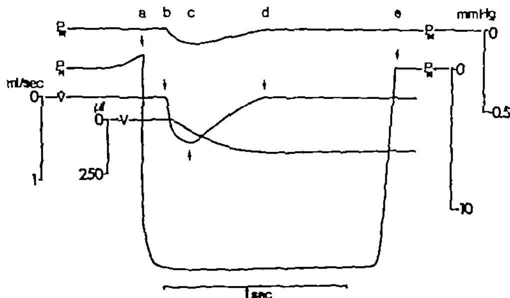


Fig. 25. Combined pressure and air flow measuring by pplication of underpressure in the nose. The pressure difference across the Et was 20 cm H_2O (14.7 mm Hg) The case was the same as in fig. 24. (For symbols see fig. 24)

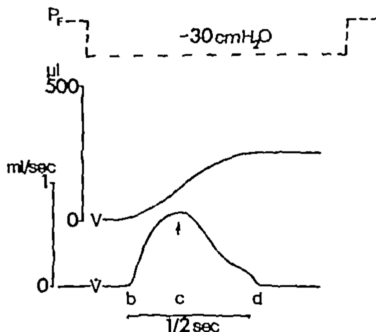


Fig. 26. Combined pressure and air flow measuring by application of underpressure in the ear The pressure difference across the Et was 30 cm H_2O (22 mm Hg) The case was the same as in fig. 24. (For symbols see fig. 24)

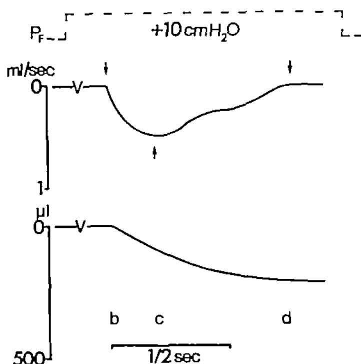


Fig 27 Combined pressure and air flow measuring by application of overpressure in the ear The pressure difference across the Et was cm H_2O (7 3 mm Hg) The case was the same as in fig. 24 (For symbols see fig. 24.)

Table XXI. *Maximal air flows and corresponding air flow resistances in the case illustrated in figs. 24–27* (italics = calculated air flow resistance values in figs. 24–27)

	V ml/sec.			R cm H_2O/ml/sec.		
	Δp cm H_2O			Δp cm H_2O		
		20	30		20	30
Aspiration	0.36	0 62	0.70	28	32	43
Inflation	0.39	.0	2.0	26	20	*15*
Underpressure in the nose	3	0.54	0 51	32	37	49
Deflation	.45	50	–	22	3	–

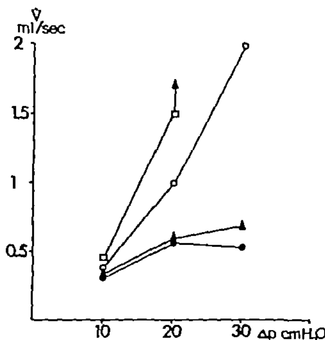


Fig. 28. Air flows through the Et in the same patient as shown in figs 24–27 t different Et testings.

●—● Underpressure applied in the nose
○—○ Overpressure applied in the nose (graded inflation)
▲—▲ Underpressure applied in the ear (aspiration)
□—□ Overpressure applied in the ear (deflation)
(Arrow indicates spontaneous emptying)

well as by aspiration testing in a patulous tube case, the maximal and level air flows together with the corresponding air flow resistance values were calculated (Table XXIII)

A comparison between air flow resistances at level air flow during graded inflation in a patulous tube case (Table XXIII) and a case with poorly functioning Et (Table XXII) shows much lower values in the patulous tube case.

CONSTANT UNDERPRESSURE APPLICATION IN THE MIDDLE EAR

In fig. 33 it is shown how the air flow resistance changed when an underpressure of 30 cm H_2O was applied in the middle ear for 25 minutes. The patient was instructed to swallow every fifth minute to equilibrate the underpressure. After 25 minutes there was no equilibration. When the underpressure was released the patient could again equilibrate. The air flow resistance returned successively

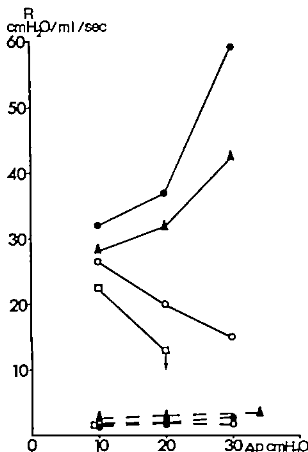


Fig. 29 Air flow resistances of the same patient as shown in figs. 24–27 and in a patulous tube case at different Et testings. (For symbols see fig. 28) Continuous line – case of chronic otitis media (L.R. 400513 ♂) Interrupted lines – patulous tube case (E.A. 08 027 ♂)

to a normal value During the testing of the patulous tube cases however very small changes in the air flow resistance of the Et were obtained during the same procedure.

TUBAL OPENING PERIOD

At air flow measuring with underpressures in the ear the tubal opening time was measured in 13 cases. The times varied between 0.2 and 0 9 sec. with a mean value of 0 36 sec. and a standard deviation of 0.21 Every opening time was a mean of 3 measurings (at 10 20 and 30 cm H_2O pressure difference across the Et) Very small variations between tubal opening times in the same patient at varying pressure differences were found.

Earlier investigators found similar tubal opening times. Thus Perlman (1951) found tubal opening times of 0 16 0.20 0 16–0 60 sec. using a sound conduction

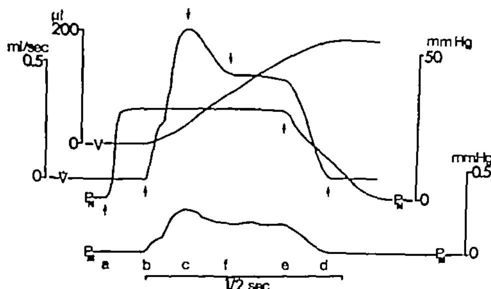


Fig. 30. Recordings from a case of chronic otitis media tested with graded inflation. To get tubal passage a pressure difference across the Et of 40 cm H_2O (29.4 mm Hg) was demanded. (For symbols see survey of symbols p. 7.) At the arrow indicated by the letter f a level in air flow curve was obtained.

Table XXII. *Maximal air flow and level air flow with corresponding resistances in the case illustrated in fig. 30*

	Graded inflation (Δp = 40 cm H_2O)	
	Maximal air flow	Level air flow
V ml/sec.	63	0.43
R cm H_2O/ml/sec.	63	93

technique. Miller (1965) reported values varying between 0.12–0.50 with the mean of 0.24 sec. Aschan (1955) obtained tubal opening times of 0.25 sec. determined from X-ray investigation of the Et with contrast media.

AIR VOLUMES PASSING THROUGH THE EUSTACHIAN TUBE

At aspiration testing, the air volumes passing through the Et in one case with chronic otitis media (capable of equilibrating an underpressure) and in one case with a patulous tube, were compared at the same pressure difference (30 cm H_2O across the Et) (Table XXIV). The periods during which the tubes

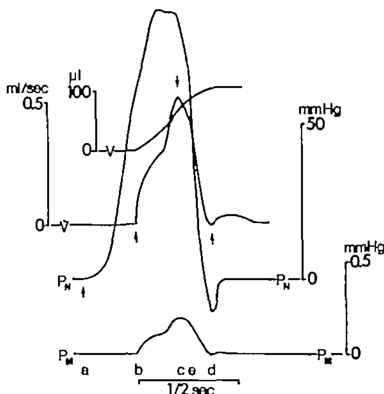


Fig. 3 Recordings from a case of chronic otitis media with a poorly functioning Et only inflatable be Politzer method. (For symbols see survey of symbols p 7)

were kept open during swallowing in the case with chronic otitis media were 0.5 0.5 and 0.5 sec. and in the case with patulous tube 0.42 0.5 and 0.5 sec. The air volumes were largest in the patulous tube case which means a lower air flow resistance in spite of identical tubal opening times and pressure differences across the Et.

PATULOUS TUBE CASES

Zöllner (1942) pointed out that in cases with chronic otitis media a higher incidence of patulous tube conditions are found than in normal ears The author's attention was drawn to cases where patulous tube was suspected on anamnestic grounds. Several such cases were found during ear manometry

The ears with patulous tube were investigated in two groups. One of the groups was tested for the capacity for equilibrating an applied underpressure in the middle ear The other group was tested by air flow measuring

In patients with patulous tubes the Et generally closes when the patient is placed in a horisontal position. When closure of the patulous tube was effected

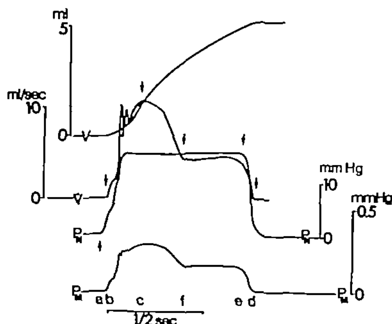


Fig. 32. Recordings from a patulous tube case at testing with graded inflation t a pressure difference of 20 cm H_2O (14.7 mm Hg) across the Et. (For symbols see survey of symbols p. 7.)

T ble XXIII. *Air flows and corresponding resistances in a patulous tube case (E. A. ♂ 081027) tested by inflation and aspiration methods.* (Pressure difference across the Et 20 cm H_2O.)

	Graded inflation		Aspiration
	Maximal air flow	Level air flow	Maximal air flow
$\dot{V}$ ml/sec.	0.3	4.4	7.4
R cm H_2O/ml/sec.	9	4.8	2.7

testing with the aspiration method could be performed after ear drum incision. Five of the six cases investigated in this way succeeded in equilibrating under pressure in the middle ear. They all did it directly to o-level. One patient who had been *operated on as a child for a cleft palate could not do this.*

The other patulous tube group (7 cases) was investigated by the method for determination of tubal airway resistance. All the resistance values at the different tubal function testings were considerably lower than those for the other ears (see figs. 20–29 and Table XVI).

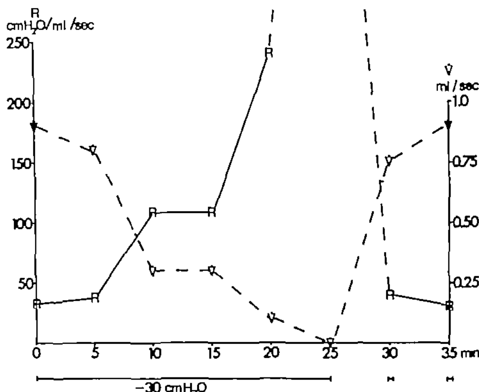


Fig 33. Air flow and corresponding resistance changes in a case of chronic otitis media at application of underpressure of 30 cm H_2O in the ear for 25 minutes. The patient was instructed to swallow only every fifth minute.
|——| applied underpressure in the ear

Table XXIV *Air volumes passing through the Et at deglutition by aspiration testings on 2 typical cases.* (Pressure difference across the Et was 30 cm H_2O)

	V microlitres
Chronic otitis media (L.R. ♂ 400513)	188 205, 223
Patulous tube (E.A. ♂ 08 027)	2505, 3006, 3173

Example of recording on a patulous tube case is given in fig 34. Simultaneous pressure variations are seen in the nose and in the middle ear In the illustrated case the air flow resistance was 1 7 cm H_2O/ml/sec. in the middle of the inspiration.

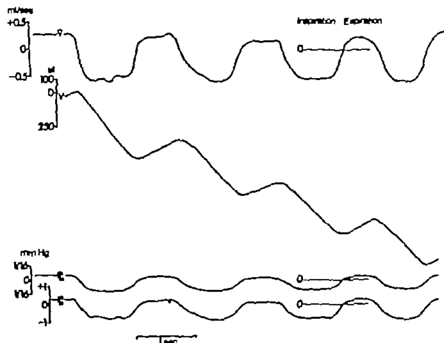


Fig. 34 Recordings from a case of patulous tube by combined pressure and ir flow measur ings. The volumes of air passing th tube are larger t inspiration than at expiration which gives the slope of the integrated curve

Discussion

The Et is normally closed i. e. the closure forces exceed the opening forces owing to a spring effect exercised by the cartilage and the surrounding tissues. During deglutition, opening may appear allowing a pressure equilibration if there is a pressure difference across the Et. Such a pressure difference is normally a result of the underpressure arising in the closed air space of ear The normal direction of air flow is thus from the rhinopharynx to the ear For this reason the aspiration method devised by the author should be a physiological method for testing the Et function

In the comparison between normal ears and ears with chronic otitis media a great difference in their capacity for equilibrating underpressures applied in the middle ear was established Among the ears with chronic otitis media a large number could not perform this while all normal ears could.

The reason why many ears were unable to equilibrate is bound up with factors which regulate the ventilation through the Et. If equilibration does not take place the balance between opening and closure forces has been disturbed. The muscle activity cannot overcome luminal or extraluminal factors which keep the Et closed. There is then a blockage of the Et which may be of a reversible or a permanent type.

REVERSIBLE BLOCKAGE

The commonest type is the reversible one which is seen during infections of the nose and the upper airway when swelling of the mucous membrane of the Et takes place preventing normal tubal ventilation. This may result in acute inflammation of the tube and the middle ear During mucosal catarrhs increased secretion may contribute to blockage of the tube particularly if the secretion is of a very thick and viscous type.

After X ray treatment of tumours in the nose, pharynx or throat serous otitis may appear This depends mainly on mucosal transitory swelling of the tube.

It is also well known that mechanical obstruction caused by adenoids often interferes with the Et function. This function mostly becomes normal after removal of the adenoid.

PERMANENT BLOCKAGE

After middle ear inflammations chronic membrane changes may occur in the shape of adherences and thickening of the mucous membrane of the middle

ear and probably also the Et. Different degrees of permanent tubal stenosis may then appear making it difficult for the Et to open effectively

Repeated testings with unchanged results make it possible to state that the blockage in cases of chronic otitis media preventing normal ventilation through the Et depends on stenosis of a permanent type.

While the aspiration method revealed a high number of ears with a poorly functioning Et in chronic otitis media the same result could not be obtained simply by using the inflation method. Passage through the Et could be obtained by using these latter methods (graded inflation and Politzer s method) in all cases if sufficiently high pressures were applied. But simply forcing air through the Et does not reflect its physiological function. The degree of stenosis cannot be exactly assessed even if the threshold pressure for obtaining passage affords some information about the tubal resistance to the air flow

Toynbee s manoeuvre gave negative results also for normal ears. Ingelstedt and Örtegren (1963) made studies using Toynbee s manoeuvre and the pressure changes caused by it in the nose and the middle ear They found that an underpressure generally appeared in the middle ear at Toynbee s manoeuvre but positive pressures as well as zero pressures could occur in spite of the fact that there had been a passage. In a number of ears a normal Et function based on Toynbee s manoeuvre may thus go undetected. Therefore this method must be considered as uncertain if the result is negative

For evaluating the graded inflation method clinically it must be of great interest to compare it with the aspiration method. The author found that cases which could equilibrate an underpressure in the ear also had a tubal passage at graded inflation with an overpressure in the nose below 10 cm H_2O For this reason the author has chosen the upper level of 10 cm H_2O as a standard for clinical evaluation of the Et function with this method. This value is further in good conformity with the results of other investigators (Zöllner 1942 van Dishoeck 1947 Thomsen 1957) In clinical work the graded inflation method could then be regarded as a supplement of the aspiration method.

During ear manometry it was observed that in some cases the equilibration could occur in small stages. The volume of the ear-manometer system must be constant during the actual investigations before the ventilatory capacity of the Et from the type of equilibration could be estimated. At the present investigation the measuring system was always the same. The volumes of the air cell system that were determined in cases with chronic otitis media varied within narrow limits (differing very little from values given by Flisberg and Zsigmond 1965) The pressure recording during equilibration may in this way give an estimation of the individual capacity of the Et for ventilating the middle ear Equilibration taking place in small stages seems to indicate greater difficulties in middle ear ventilation. One case which could equilibrate an underpressure did so in very small stages at repeated testings. This patient had very high air flow resistance values suggesting real organic stenosis. Myringoplastic surgery had earlier been

performed twice without success Insufficient Et function was almost certainly the reason for the operative failures

The aspiration and the inflation methods afford some information about the ventilation of the middle ear By using principles currently employed in respiratory physiology *it was possible to obtain further information about the mechanism* which may influence this ventilation.

During the measurements the system must be kept open. This does not reflect the normal state of the middle ear because of the necessary perforation of the ear drum. The ventilatory function of the middle ear however is very complex owing to the interplay of factors i. e. the ear drum and the air cell system (Flisberg Ingelstedt and Örtegren 1963) These factors are mainly eliminated by keeping the measuring system open Therefore the present investigation only concerns the function of the Et.

At very high air flow velocities through a tube the dynamic pressure can increase and obviously reduce the static pressure If then the static pressure becomes lower than the pressure outside an elastic tube wall a tendency to closure of the tube appears.

Yet theoretical considerations and all practical investigations strongly suggest that the dynamic forces are small as compared with the static forces during air flow through the Et. Therefore it is reasonable to assume that the dynamic forces in the Et are negligible A static pressure component, however may affect the Et to a very great extent.

At testing procedures the pressures applied in the nose or ear create varying pressure differences across the Et. When the Et is opened at deglutition this static pressure may influence the walls as a transmural pressure difference. If the Et cannot be opened by the muscular forces the static pressure can contribute to opening it. This is exemplified by the Politzer's inflation manoeuvre as well as by overpressure application in the middle ear Though the applied pressures may be unphysiological they provide accessory information about the Et at air flow measurements.

During graded inflation tests reduction of the air flow resistance was regularly found with increasing pressure differences across the Et. By application of graded underpressure in the nose, however an increasing air flow resistance could be stated.

The reason for this difference in resistance is the influence of the static pressure on the elastic walls of the Et. Positive pressures in nose or ear give a dilatation of the lumen Negative pressures on the other hand, tend to close the opened Et.

At a sufficiently high overpressure in the nose the Et could even be kept open after the deglutition. This means that the static intraluminal pressure counterbalances the closing forces of the tissue. The shape of the air flow curve during such inflation tests appears from figs. 30 and 32. Owing to the muscle contraction at the deglutition the Et opens and the air flow starts and rapidly

reaches a peak (phase b–c) When the muscle relaxes the Et tends to close (phase c f) If however the pressure is greater than the closing forces a flow level is obtained (phase f-e) When the pressure applied in the nose is then reduced the air flow curve shows the closure of the Et.

Capacity for keeping the Et open and getting an air flow level was naturally always seen among patulous tube cases but also in ears with a poorly functioning Et. The pressure needed to get such a flow level was small in patulous tube cases but high in ears with a poorly functioning tube owing to resistance differences

The long time effect of underpressure application (–30 cm H_2O) in the middle ear was also studied. (The magnitude of this underpressure was chosen after van Dishoeck's observation (1941) that down to –50 — –60 cm H_2O underpressure could be found in the middle ear) The Et then locked and equilibration was impossible. The reason may be a sucking effect on the mucous membrane which produces swelling and a transitory blockage at the aural end of the tube. After release of the underpressure the Et opened immediately indicating that a venous congestion was the reason for the locking.

The only possibility to get information about the air flow resistance in cases with poorly functioning tubes is forcing air through the Et. Even the incapacity to equilibrate tells us that the Et function is reduced. By the inflation method it was further proved that a high inflation pressure was needed to reach passage. At pressure flow measurements it was possible to state that these tubes had higher air flow resistances than those found in normal functioning ears. These high air flow resistance values seem to be due either to luminar pathological changes i. e. in the mucous membrane or to extraluminal factors i. e. muscular weakness or other tissue changes

THE PATULOUS TUBE STATE

If patients with patulous tubes lie down the Et generally closes. Increased venous pressure in the mucous membranes and peritubal tissues is probably the reason for this In this position all cases examined, except one could equilibrate an underpressure in the ear This finding illustrates a normal muscular opening function of the Et. The equilibration in all these cases took place directly to o-level, which means a widely open tube during deglutition.

One patient—earlier operated on for a cleft palate—could not equilibrate underpressure The muscle function of the Et and the soft palate must in that case be considered to be insufficient.

At testing for determination of the air flow resistances which was performed in a sitting posture the resistance values were found to be low The Et could however be sucked close at aspiration testing and at application of underpressure in the nose. This is in good conformity with the sniffing a procedure

practiced by patients with patulous tubes in order to close the Et and get rid of the symptoms

NEGATIVE DIP PHENOMENON

The author has earlier (1963) described a phenomenon called the negative dip phenomenon. The observations were confirmed in the present investigation. The dip may appear at deglutition as a negative pressure spike in the closed ear without pressure equilibration The phenomenon is interpreted as follows a small rapid pressure change is caused by a volume increase in the middle ear cavity This volume increase is due to a small separation of the mobile walls of the upper part of the Et probably caused by a tubal muscular effect. The small pressure spikes may counteract the opening of the Et. In ears with big air cell systems and normal drums the effect may be quite negligible. In cases with small air cell systems and drums which lack the damping capacity however the spike may contribute to the locking of the tube

TUBAL OPENING TIME

By recording of the tubal opening time it is possible to distinguish between an active and a passive period. The active opening period is the time during which the muscle activity can keep the tube open. In fig. 24 this period corresponds to phase b–c. In this phase however the inflation pressure must also play a part in the opening act. The active muscular opening period can also be followed by a passive opening phase. In the air flow curve this may be recorded as a level. At inflation tests the tubal opening time may then vary depending on the time during which the overpressure can be kept in the rhinopharynx. At the aspiration test, however the active opening period appears more distinct and may sometimes perhaps be shortened by the negative static pressure effect on the tubal walls.

AIR VOLUMES PASSING THE EUSTACHIAN TUBE

Because of the prolonged opening time during inflation testings it is possible to force large and varied volumes of air through the Et.

At the aspiration test, however the opening times were very constant for every individual. The author compared two cases (one patolous tube case and one case of chronic otitis media) with the same tubal opening times. At the same pressure difference across the Et greater air volumes passing through the Et in the patolous tube case were found indicating a wider tube.

It is a complex problem to reach successful operative results at myringoplastic operations, and several factors are at work. One of these factors is the ventilatory function of the Eustachian tube. This function must be normal i. e. the

patient should be able to equilibrate an underpressure in the middle ear. From the author's comparison between different clinical tubal function methods it has been made clear that a tubal passage obtained at graded inflation with a pressure less than 10 cm H_2O also means a good Et function.

A poor Et function—at repeated testings—is a very strong reason for avoiding an operation with the present available methods for closing an ear drum perforation.

Other factors essential for the operative result are the size of the perforation at the repair, the patient's age and wound healing capacity, changes of the structures in the middle ear and possibly also the size of the air cell system (Flisberg, Ingelstedt and Örtegren 1963).

A well developed air cell system—acting as an air chamber—may thus probably reduce the underpressure originating in the air space of the ear and lessen the risks of postoperative complications. The future development will perhaps provide possibilities of enlarging small air cell systems (Flisberg, Ingelstedt and Örtegren 1963, Grahne 1964).

In some of the cases of chronic otitis media the central drum perforation should perhaps be looked upon as the last remaining chance of keeping pressure normal in the middle ear and thereby bring about "healing" of the middle ear process. After closure of the perforation a loading of the middle ear may take place, i.e. due to primary tubal blockage or to tubal locking at infection of the upper airways or even locking because of the hydrostatic swelling of the tubal mucous membrane occurring in a recumbent position. Transudation and inflammation of the middle ear may be the consequence. It is well known that a serous otitis can occur after blockage of the Et. Such a condition can however be made to disappear by treatment with a plastic tube through the ear drum according to Armstrong (1954) (the method already described by Politzer 1887), thus making artificial ventilation possible for the middle ear.

The future follow-up of cases operated on with myringoplastic methods and with preoperatively tested Et function will answer the question whether now available methods for clinical Et function testing are sufficient and whether the limits for these testings are correct.

Summary

The present work was undertaken as a study of the ventilatory function of the Et by different methods and in view of underlying physiological factors It must be of the greatest importance for microsurgery of the middle ear that the Et function can be accurately estimated before an operation is considered.

The investiation has been restricted to ears with drum perforations or ears where perforations were produced by drum incision.

METHODS WORKED OUT BY THE AUTHOR

EAR MANOMETRY

This method implies that pressure changes in the closed ear—manometer system induced by deglutition are taken as an expression of the capacity of the Et to ventilate the middle ear This method has not earlier been used for testing the Et function.

By application of underpressure in the ear and testing the patient s capacity for equilibrating, the method reproduces normal ear conditions The procedure has been called the *aspiration method*

By application of positive pressure in the ear the capacity for equilibrating such pressure at deglutition was studied. This procedure has been called the *deflation method*

EVALUATION OF AIR FLOW DIRECTION

By using a highly amplified manometer system airtightly connected to the external ear canal the direction of air flow at different experimental conditions could be analysed. The system could be closed or kept open. The method implies observations of very small air flows through the Et.

COMBINED PRESSURE AND AIR FLOW MEASUREMENTS

This method was based on principles used in studies of respiratory air flow The method has not earlier been used for otological purposes

After calculation of the air flow (V) passing through the Et and determination of the pressure difference (Δp) across the tube the air flow resistance (R) could be estimated according to the formula $R = \frac{\Delta p}{V}$

OTHER METHODS USED

Politzer's method for obtaining tubal passage.
Application of graded over or underpressures in the nose
Toynbee's manoeuvre

RESULTS

One hundred and two ears with chronic otitis media and 36 healthy ears were investigated by ear manometry The testings were repeated in the ears with chronic otitis media.

It was found that all healthy ears could equilibrate over as well as under pressures that were applied to the ear

In the series of ears with chronic otitis media only 42 % could equilibrate an underpressure while 58 % could equilibrate an overpressure applied in the ear

The differences between normal ears and ears with chronic otitis media probably depend on tissue factors for example mucous membrane changes with thickening and adherences which prevent opening of the Et in a large number of such ears These ears would be regarded as unsuitable for tympano- and myringo-plastic surgery with the methods hitherto used.

By testing with different inflation methods (Politzer's method and graded inflation) it was found that at a sufficiently high pressure in the nose a passage through the Et normal or not, was produced at deglutition

These methods supply information about the capacity to obtain passage through the Et but no data on the function of the Et. At graded inflation the upper pressure limit for getting passage in normal ears was below + 10 cm H_2O

In ears with chronic otitis media it was possible to obtain a passage by the inflation method at a pressure threshold below 10 cm H_2O in the same cases that could equilibrate an underpressure applied in the ear This suggests that the upper limit of 10 cm H_2O for graded inflation could be regarded as a sign of acceptable Et function.

As it is impossible to grade the pressure for obtaining passage with Politzer's method this method must only be regarded as one way of obtaining information about the capacity for getting passage or not through the Et.

By Toynbee's manoeuvre it was found that a great many ears with chronic otitis media but also normal ears lacked passage This means that this method must be considered uncertain.

Among the 102 cases with chronic otitis media there were 6 ears with patulous tubes. By placing these patients horisontally the Et was closed Testing with ear manometry could then be performed. Five of these cases could equilibrate an underpressure. This supports the assumption that one of the reasons for the condition of patulous tube in these cases was mainly some tissue factor probably bound up with the tubal mucosa while the muscle function was intact.

When there is an increased tendency in the mucous membranes of the Et to stick together attempts to open the Et are often unsuccessful A slight opening of the aural portion of the Et produced during deglutition gives a simultaneous increase of the closed air volume in the middle ear This has earlier been observed by the author during ear manometry and was called the negative dip phenomenon In the present investigation it was possible to verify the presence of this phenomenon The negative pressure spike was further found also in normal ears with no sign of infection and probably without any marked tendency in the mucous membrane to be glued together

Measuring of the air flow resistance of the Et was performed in 39 ears with chronic otitis media 2 ears with chronic otitis media with patulous tubes and 5 ears with symptoms of patulous tube with intact ear drums. In the last cases incision of the drum was performed. The presence of patulous tube was verified by ear manometry

The cases were divided into 3 groups

Group I Cases which could equilibrate an underpressure in the middle ear (20 ears)

Group II Cases which could not equilibrate an underpressure in the middle ear (19 ears)

Group III Cases of patulous tube (7 ears)

By testing with graded inflation the resulting air flow resistances were found to be different in the various groups Group I had resistance values between 5 and 50 cm H_2O/ml/sec Group II values between 50 and 200 cm H_2O/ml/sec Group III values below 5–6 cm H_2O/ml/sec.

During the inflation testing of group I it was found that the air flow resistances diminished with increasing pressure differences across the Et.

During application of underpressure in the ear (aspiration testing) or application of underpressure in the nose the air flow resistances were found to increase slightly with increasing pressure differences across the Et.

The resistance changes seem to be due to the influence of static pressure on the tubal walls. At graded inflation testing a dilatation of the Et appears while at underpressure application in the ear or the nose a certain narrowing of the lumen may take place.

During air flow from the middle ear to the rhinopharynx it was shown that the air flow resistances at application of underpressures in the nose were higher than those at testing with application of positive pressure in the ear

By exposing the middle ear to underpressure (– 30 cm H_2O) it was possible to prove that the Et could be locked for air passage at deglutition in certain ears. After 5–10 minutes the locking had disappeared. This indicates that the reason

was venous congestion of the mucous membranes. The investigation simulated pathological conditions in the ear

The duration of the air flow period was taken as the tubal opening time when aspiration testings were performed. The time values were very constant for every individual but differed widely from one case to another (mean value 0.36 sec., standard deviation 0.21)

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Table XXV *Primary ai flow values at the testing of group I with application of overpressure in the nose* (graded inflation)

Patient		V ml/sec.			
		Δp cm H_2O			
			20	30	40
LS	3 1220 ♀	.22	2.0	5 0	–
G.B	460906 ♂	1.25	2.30	3.6	5.4
J.A.	49 028 ♀	0.42	1.0	5	3.7
H.A.	140219 ♂	0.66	1 50	2.5	5 0
A.H.	200907 ♂	0.66		1.9	–
L.R.	400513 ♂	0 39	1.0	2.0	–
L.N.	510808 ♀	0.55	1.40	2 9	–
S G	180826 ♀	0.22	.80	1 9	–
T.L.	25 015 ♂	0 21	0.50	0.8	.0
S.E.O	310524 ♂	0.28	0 53	1.0	–
H.H.	0 0707 ♂	0.58	1.30	2 3	–
V.S	380322 ♀	0.37	0.65	1 5	–
M J	38 207 ♀	1 50	3.00	5.8	8 5
H.B.	990627 ♀	0.26	0.80	1.5	3 2
S M.	200915 ♀	0.28	0 80	1 3	–
L.O	200904 ♀	.80	3 30	3 8	5 8
K.N	530 09 ♀	0 33	75	1 3	–
B.A.	45 6 ♀	0.33	.92	2.0	–
A J	450426 ♀	0.72	2.50	4 5	–
M.B F	230809 ♀	0.07	0.12	0.20	0 24
Mean air flow		0 58	38	5	4.8
Standard deviation		± .46	±0.84	±1.2	±2.1

excluded in the statistical analysis.
testing not performed.

Table XXVI. *Primary air flow values at the testing of group I with application of under pressure in the nose*

Patient			V ml/sec.		
			Δp cm H_2O		
			10	20	30
J.A.	49 028	♀	–	0.42	0.50
A.H.	200907	♂	.20	0.30	–
G.B.	460906	♂	0.60	0.66	0.66
L.R.	400513	♂	0.31	0.54	0.51
L.N	510808	♂	0.59	0.70	1.60
S.G	180826	♀	0.27	0.42	0.42
S.E.O	310524	♂	0.29	0.37	0.48
H.H.	010707	♂	0.66	0.41	0.33
M.J	381207	♀	1.80	2.20	2.90
*T.L.	251015	♂	0.05	0.05	–
M.B.F	230809	♀	0.1	0.17	0.20
Mean air flow			0.60	0.68	0.87
Standard deviation			±0.52	±0.59	±0.77

excluded in the statistical analysis.
no passage reached.

Table XXVII. *Primary air flow values at the testing of group I with application of under-pressure in the ear* (aspiration)

Patient			V ml/sec.		
			Δp cm H_2O		
			10	20	30
I.S.	3 1220	♀	0.18	0.27	35
G.B.	460908	♂	0.83	2.50	1.90
J.A.	49 028	♀	0.42	0.50	0.59
H.A.	140219	♂	1.1	1.90	2.40
A.H.	200907	♂	0.25	0.50	0.68
L.R.	400513	♂	0.36	0.62	0.70
L.N.	510808	♀	53	.85	.20
S.G.	80826	♀	0.24	0.37	4
S.E.O.	310524	♂	0.28	48	0.55
H.H.	010707	♂	.00	1.40	70
M.J	381207	♀	1.90	3.80	6.00
*T.L.	2510 5	♂	15	0. 0	0
*M.B.F	230809	♀	0.15	23	25
Mean air flow			64	.1	1.50
Standard deviation			± 52	± 04	± 64

excluded in the statistical analysis

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DEVELOPMENT OF THE INNER EAR OF THE MOUSE A RADIOAUTOGRAPHIC STUDY OF TERMINAL MITOSES

R. J RUBEN

ACTA OTO-LARYNGOLOGICA NARVAVÄGEN 14, STOCKHOLM NO

ACTA OTO LARYNGOLOGICA

SUPPLEMENTUM 220

DEVELOPMENT OF THE INNER EAR OF THE MOUSE A RADIOAUTOGRAPHIC STUDY OF TERMINAL MITOSES

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Dedicated to Stacy Rufus Guild
Anatomist & Teacher 1890–1966

The development of the inner ear of vertebrates has been examined in various ways During the 19th and early 20th centuries Boettcher (8) Retzius (41) Held (21) and others studied the morphological development of the membranous labyrinth. More recently Bast and Anson (5) have made major contributions to the understanding of the morphological development of the ear There have been two detailed morphological studies on the development of the inner ear of the rodent (57 58) All of these studies have demonstrated that cytological differentiation appears first at the base of the cochlea and proceeds to the apex over several days.

Ramón y Cajal (40) and Tello (54) have examined the pattern of afferent innervation of the developing inner ear of the mouse Tello observed that some of the afferent fibers innervated the basal turn before the apex. Rossi (43) studied the pattern of efferent innervation and noted that the efferent fibers to the cochlea began their innervation at the base

Experimental manipulation of the developing inner ear has long been practiced by embryologists and this work has been reviewed by Benoit (7) Among many sources of influence which contribute to the development of the inner ear are the mesenchymal and neural tissues which serves as successive inducers of the inner ear (59) There has been recent work on the histochemical differentiation of the inner ear (37 55) Kikuchi and Hilding (23) have examined the ultrastructure of the later stages of the development of the inner ear of the mouse Studies of the development of the various electrical potentials of the ear have been carried out (1 2 28, 35 36, 47) and have demonstrated that the appearance of the electrophysiological responses are correlated with the cytological differentiation of the cochlea.

Genetic anomalies have been used to study the processes involved in the normal development of the inner ear The work of Deol (11 12, 13) demonstrates that anomalies of the neural tube are associated with various malformations of the inner ear Kikuchi's and Hilding's (24) observation of a deficiency of efferent innervation in the shaker 1 mutant mouse also suggests an interrelationship between the development of the brain stem and the inner ear Ross (42) has noted central nervous system deficiencies in genetically deaf mice

The studies in this report deal with the terminal mitoses of the cells of the membranous labyrinth by analyzing radioautographs of the inner ear following labeling with tritiated thymidine during development Terminal mitoses in this study are considered to be the last divisions which a cell undergoes. The terminal mitoses serve as an index of times of the establishment of a permanent cell population. Cell division ceases for most classes

of cells in the inner ear of the mouse during gestation or soon after birth (26) The labeled cells in the adult ear represent the terminal mitoses which occurred at the time during development when the ear was exposed to tritiated thymidine The information obtained from the knowledge of the temporal and spatial patterns of terminal mitoses should be useful for the further understanding of normal and abnormal development of the membranous labyrinth

There are many reports in which this technique has been used to study the developmental pattern of terminal mitoses in other organs (3 16 22, 9 30 33 34 49 56) There is one study on the incorporation of tritiated thymidine into the ear of adult animals (26) but there are, to my knowledge no reports of tritiated thymidine radioautographic detection of terminal mitoses in the inner ear during prenatal development and early postnatal life The mouse was chosen as an experimental animal because of the large number of different strains of genetically deaf mice (51)

The present work seeks to map in time and space, the terminal mitoses of the different cell types of the membranous labyrinth, by means of labeling with tritiated thymidine The theoretical and technical aspects of this technique are reported elsewhere (9 10 14 15 22, 30 31 32, 33 34 39 46) Thymidine is incorporated into the DNA of a cell during the synthetic phase of the mitotic cycle and remains as part of the DNA of the two daughter cells. The thymidine is available to cells in the mouse for about one hour after injection (9 10 22, 29 30 34 46) If the thymidine is labeled with a radioactive molecule such as tritium then the DNA which incorporates the labeled thymidine can be located within the cell nucleus. All of the cells which are synthesizing DNA at the time when the tritiated thymidine is available will become labeled and divide Some of the labeled cells will divide only once and will have a maximum amount of labeled DNA, whereas others will continue to divide and dilute the label

After several days the animals, which were exposed to tritiated thymidine are sacrificed Radioautographs are then made by covering the tissue with a photographic emulsion, which will be exposed by the beta particles emitted from the tritium. Those cells in which labeled nuclei are detected by the radioautographs are the daughter or granddaughter cells of the cells which were in their synthetic phase during the period of exposure to the tritiated thymidine These labeled cells, in the inner ear have undergone their terminal mitoses soon after the time they were exposed to the tritiated thymidine The cells without label, or in which the label is undetectable represent those which did not incorporate the tritiated thymidine or went on to have many cell divisions after their exposure to the tritiated thymidine The times when the various cell types undergo their terminal mitoses can be established by exposing a series of animals to tritiated thymidine at different times during gestation

PROCEDURE

I Experimental Design

Fourteen pregnant CBA J mice (supplied from the Jackson Laboratory Bar Harbor Maine) under one year of age were each injected intraperitoneally with 0.6 μc of tritiated thymidine per gram of body weight The tritiated thymidine (Schwarz BioResearch, Inc.) had a specific activity of 3 curies per millimole and a concentration of 0.5 millicuries per ml In addition five litters of CBA J mice were injected subcutaneously with the same dosage of tritiated thymidine on different days after birth The day of gestation was determined by the vaginal plug method The day when the plug was observed was called gestation day 1 and the day of birth was called postpartum day 1 Fourteen of the nineteen litters had a gestation period of 20 days and five had a gestation period of 21 days The animals were exposed to tritiated thymidine at a time between 9.30 a.m and 12 30 p m on the 10th, 12th, 13th, 14th, 15th, 16th or 18th day of gestation and on the 1st 3rd, 5th or 7th day postpartum The ears of all these animals grew to anatomical maturity before they were sacrificed for examination.

Fifty three inner ears from the litters were analyzed. Table 1 shows the number of ears examined for each day on which tritiated thymidine was administered. Ears from two different litters were examined for all days from the 10th day of gestation until the first day postpartum Only one litter per day was used for the observations on postpartum days 3, 5 and The ears were identified according to litter and the ears from an individual within a litter were not separately marked. The animals were sacrificed from the 13th to the 22nd day postpartum the greatest number being sacrificed on the 15th day postpartum

II Tissue Processing

The animals were anesthetized in a chloroform bottle (45) The thorax was opened and a No 25 gauge needle was placed in the left ventricle. The animals were perfused with 10 ml of a balanced salt solution and then with an additional 10 ml of 10% Acrolein buffered with phosphate to pH 7 4 (50) The head was severed, the skin removed and the bullae and calvarium opened. The specimen was placed in the 10% Acrolein solution and kept in the refrigerator at 4 C for 24 hours. After that it was washed in tap water for one-half hour and the specimen was decalcified over a three day period by a 10% solution of disodium ethylenediaminetetraacetate (EDTA) with 2.5 or 5.0% polyvinylpyrrolidone (PVP) and buffered to

TABLE 1 *Number of Ears Exposed to Tritiated Thymidine and Length of Exposure of Emulsion*

Time of Exposure To Tritiated Thymidine	Weeks of Exposure of Emulsion					T tal Number of Ears per D y
	3	4	6	9	11	
Gestation Day						
10	1	1	1	1		4
12		2	1	2		5
13	1	1	2	3	1	8
14	1	1	2	3	1	8
15	1	1	2	2		6
16	1	1	2	1	1	6
18	1	1	2	2		6
Postpartum Day						
1	1		1	1		3
3			1	1		2
5			1	1		2
7			2	1		3
			Total Number f Ears in St dy = 53			

pH 7 4 with a Tris hydroxymethyl aminomethane buffer (4 17 20 38) The specimen was again washed in tap water for one half hour Dehydra tion was accomplished by placing the specimens for 48 hours in a 1 1 (v/v) solution of ethylene glycol monomethyl ether and methyl alcohol (50) They were placed in 2% celloidin dissolved in the 1 1 ethylene glycol monomethyl ether and methyl alcohol for 24 hours. This was followed by hardening in chloroform for 12 hours. They were then placed in 90% polyethylene glycol 400-distearate and 10% cetyl alcohol (w/w) at 37 C for 72 hours (50 52) The tissue was embedded in the polyethylene glycol 400-distearate and cetyl alcohol and was placed in the refrigerator until sectioning

III *Radioautographic Technique*

The ears were sectioned at 10 μ in a plane approximately parallel to the axis of the cochlea After serially mounting the sections in a 0 1% (w/w) gelatin solution, the polyethylene glycol and cetyl alcohol were removed with xylene and the sections were hydrated They were then dipped in a solution of one part Kodak NTB-2 emulsion and one part distilled water (v/v) at 40 C, dried for 20 minutes in a humid oven at 30 C and stored in light pr f b xes for three to eleven weeks in dry ice The length of time of exposu [illegible] s me difference in the number of labeled cells detected but this wa [illegible] h n compared to the variation between litter mates or different [illegible] ted on the same day with the same duration of ex posure o t [illegible] n

Ideal len [illegible]

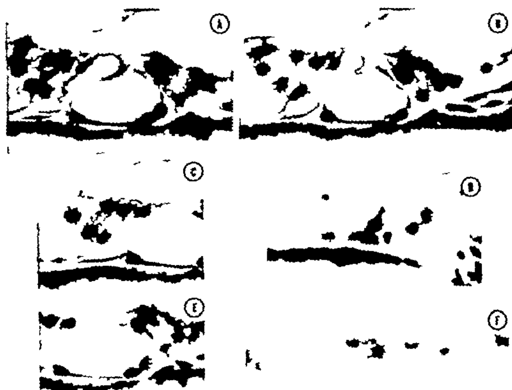


Fig. 1 Radioa tographs. 830 (*a*) Ear exposed to tritiated thymidine on the 14th day of gestation Labeled outer hair cells, Deiter' cell, internal pporting cells (*b*) Ear exposed t tritiated thymidine on the 14th day of gestation. Labeled Hensen cell, outer hair cell, Deiter' cell, i ner hair cell, internal pporting cells. ( ) Ear exposed t tritiated th midine on the 14th day of gestation. Labeled Hensen cell, Deiter' cell nd outer hair cell (*d*) Ear posed t tritiated thymidine on the 14th day of gestation. Labeled Claudius cell ( ) Ear exposed t tritiated thymidine the 14th da of gestat on. Labeled nner pilla cell (*f*) Ea exposed t tritiated thymidine on the first da postpart m. Labeled cell n R issner' membrane

After exposure the slides were developed in Kodak Dektol developer fixed with hypo, washed in distilled water and stained with toluidine blue Examples of the radioautographs are illustrated in Figures 1 2 and 3

IV Methods of Observation

Every fourth section was examined. Eighteen cell types were studied in the cochlea and 20 cell types were studied in the vestibular apparatus (Table 2) The cochleae were reconstructed using the methods of Guild and Schuknecht (18, 19 48) This method projects the turns of the cochlear spiral onto a common plane perpendicular to the axis of the cochlea. A modification was made in order to incorporate cells further from the modiolus than the outer hair cells. The modification was that the tangent of the external sulcus cells was used instead of the tangent of the outer

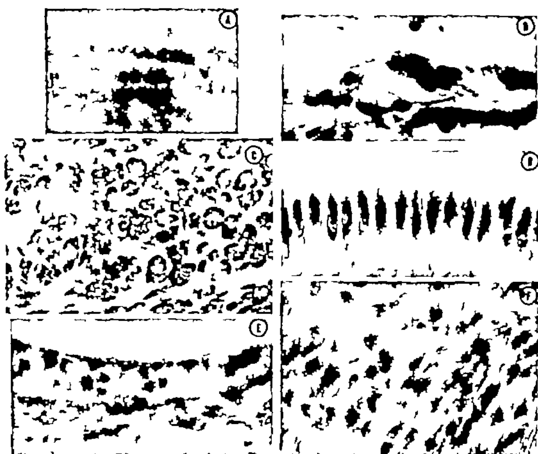


FIG. 2. Il dioautographs. 830 ( ) Ea exposed t tritiated thymidin on the 12th day f gest ti n. Labeled outer hair cell apical turn (*b*) Ear xposed to tritiated thymidi n the 16th da of gestati n. Labeled outer hai cell, Deiter's cell d epithelial cells f basila membra t the basal turn. ( ) Ear xposed t tritiated thymidi e the 14th day f gestati n. Labeled piral gangli n cell (*d*) Ea exposed t tritiated thymdi the 16th day f gestatio Labeled cell f th pithel m f the limbus. ( ) Ear xposed t tritiated thymidine on th first day postpartum Labeled cell f the stria v scul ri nd the spiral ligament (*f*) Ea e posed to t itiated thymidine on the first day post part m Labeled cell f the spiral ligam nt.

hair cells to determine the radius of each turn. An individual reconstruction was made for each cochlea based on the tangents of the external sulcus cells. Nine copies of this reconstruction were made and the 18 cell types were plotted in pairs on these reconstructions. Figure 4 represents the reconstruction for animal no 2044E-1 of the inner and outer hair cells. *One to five observations were made from each section, depending upon the* number of times the cochlear spiral was intersected by the plane of the section (Fig. 4) If the section was near the modiolus, i.e., mid modiolar as many as five separate observations could be made, as five different portions of the cochlear duct were observed in the section (e.g Fig 4 section no 50) If the section was taken at some distance from the modiolus

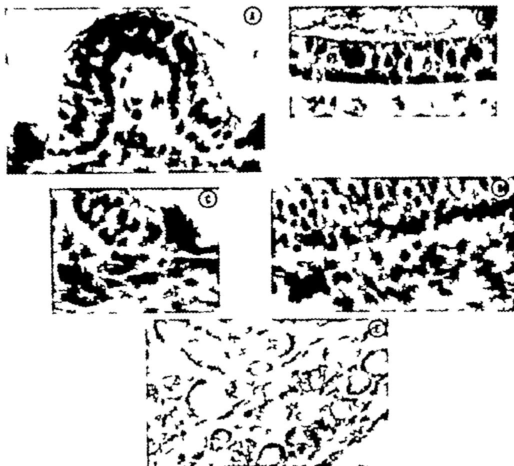


FIG. 3 Radioautogr phs 840 (*a*) Ea exposed t tritiated th midine on the 18th da f gest tion. Labeled hai nd pporti g cells f the crista f the terior semi-ircula canal (*b*) Ear exposed to tritiated thymidine on the 18th day of gestation. Labeled ha nd pport g cells of the macula of the saccule. ( ) Ear exposed t tritiated thymidi on the first da postpart m. Labeled epithelial nd connecti tissue cells of the crist of the anterior semi-circul canal. (*d*) Ear exposed t tritiated th m dine n the first da postpart m. Labeled connectiv tis cells of the macul f the tricle (Ea exposed to tritiated thymidine on the 13th day of gestation Labeled Scarpa ganglion cells.

(e.g Fig 4 section no 10) then only one observation was made because the section cut through only one portion of the cochlear duct At each observation point the total number of cells in each class and the number of labeled cells in each class (or in some instances, only the number of labeled cells) was recorded. If the cell type in question was not present at the observation point a zero was recorded. For example in Figure 4 zeros a e f und at section no 10 since the inner and outer hair cells were not present.

The total number of cells, and the number of labeled cells at each ob-

TABLE 2. *Cell Types Examined*

Cochlea
- Inner hair cells
- Outer hair cells
- Inner s pporting cells of inner hair cells
- Deiters cells
- Inner pillar cells
- Outer pillar cells
- Claudius cells
- Hensen cells
- Internal sulcus cells
- External sulcus cells
- Reissner's membrane
- Epithelium of basilar membrane
- Stria vascularis
- Spiral ligament
- Limbus epithelium
- Limbus stroma
- Spiral ganglion cells
- Schwa n cells

Saccule
- Hair cells
- Supporting cells
- Con ective tissu

Utricle
- Hair cells
- Supporting cells
- Co nective tissues

Anterior Crista
- Hair cells
- Supporting cells
- Epithelial cells
- Connective tissue

Horizontal Crist
- Hair cells
- Supporting cells
- Epithelial cells
- Connective tissue

Posterior Crista
- Hai cells
- Supporting cells
- Epithelial cells
- Con ecti e tissu

Scarpa s ganglion
- Ganglion cells
- Schw nn cells

servation point in the reconstruction, was determined for each of the following cell types inner hair cells, outer hair cells, inner supporting cells, Deiter s cells, inner pillar cells, outer pillar cells, Claudius cells, Hensen s cells, spiral ganglion cells, internal sulcus cells and external sulcus cells. Only the number of labeled cells was counted for Schwann cells, cells of Reissner s membrane epithelial cells of the basilar membrane [1] cells of the stria vascularis, cells of the spiral ligament, epithelial cells of the limbus and cells of the limbus stroma.

Analysis of the reconstruction was made with the aid of a computer program. The number of observations of a given cell type within a cochlea was considered to be proportional to the length within the cochlea of the tissue containing that cell type Those cell types which were further from the m diolus subtended the greatest area and were distributed ov r a greater length than those which were distributed closer to the modiolus (e g the number of bservations for the spiral ligament was much greater than that of the ral g n cells) The data for the cochlear reconstructions were transfe ed to cards and the informati n was processed so as to

[1] The l l ell l b are f nd n the scala tympani a pect f th ba ll me

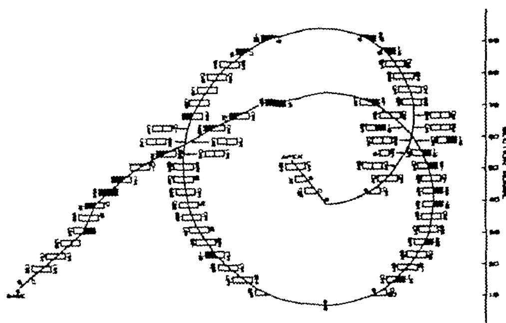


FIG. 4 Cochlea reconstructi n of ex no. 3644E-1 Outer hair cell are tabulated on the outsid and inner hair cell on the i ide of the piral. The denominator is the number f cells present and the numerator the number of labeled cell present. Filled-in boxes indicated that labeled cell were present

tabulate, for each cell type within the cochlea, the number of cells present, the number labeled, and the number of labeled cells divided by the number of cells present (percent labeling) In the classes of cells in which only the number of labeled cells were counted, a +1 was recorded at *those* observation points at which the cell was present The computer program was so designed as to eliminate observation points which had a zero in the "cell present" category and compress the remaining observations. These remaining observations were then defined as the total "distance" that a particular cell type was found within the cochlear duct This length was given the arbitrary value of 1 0 The first observation nearest the basal turn was given the value of 0 and all distances between the base and apex were expressed as a fraction of 1 0 Thus the distance 0 to 0.2 would en compass the first 20% of those observations from the beginning of the basal turn in which there were no zeros recorded.

The distribution of the cells could be divided into 1 to 36 segments of equal length starting at the base and ending at the apex. Two examples of h w th computer program worked are given below First, visualize a chlea in which two cell types, A and B, are to be considered. This cochlea is to be divided into quarters There were 100 observations for cell type A

TABLE 3 *Example of Computer Program*

Computer Input

Observation Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Number of Cells Present	0	0	2	2	2	3	0	0	3	2	2	2	0	2	0
Base															Apex

Computer Output

I. Compression of *Observations and* Elimination of Zeros	New Observation Number	1	2	3	4	5	6	7	8	9
	Number of Cells present	2	2	2	3	3	2	2	2	2
	Base = 0.0					0.5				1 0 = Apex

II. Number of observations at which cells were present = 9

III. Divide int two segments:

9/2 = 4.5 bservations per segment

IV Calculation of number of cells present in each segment.

First segment (0 0 to 0.5) Total of first 4.5 observations

Second segment (0.5 to 1 0) Total of second 4.5 observations

New Observation Number	Number of cells Present	New Observation Number	Number of cells Present
1	2	5	1.5 = (3/2)
2	2	6	2
3	2	7	2
4	3	8	2
5	1.5 = (3/2)	9	2
	10.5 cells present from 0.0 to 0.5		9.5 cells present from 0.5 to 1 0

and 40 observations for cell type B The first quarter 0 0 to 0.25 would include the first 25 observations for cell type A and the first 10 observa tions for cell type B The second quarter 0.26 to 0.5 would contain the observations from the 26th to 50th observation point of cell type A and the 11th to 20th observations for cell type B, etc. The computer program was so arranged that if a segment ended so that it would contain a fraction of an observation, then the number of cells in the observation would be divided proportionately between the two segments. Table 3 illustrates an example of this feature of the computer program This hypothetical cochlea has fifteen observation points. The cell type which was examined was found in nine of these observation points. The cochlea was divided into two equal segments, and the first segment contained one half of the observations. These were the number of cells to be found at the first four and a half observatic n p ints Th observations of the first four points with half of

the observations at the fifth observation point were added to give a total of 10.5 cells in the basal half (0.0 to 0.5) of the cochlea. The remaining one half of the cells present at the fifth observation point were added to the number of cells found at the remaining four observation points to give a total of 9.5 cells in the apical half of the cochlea, i.e., from 0.5 to 1.0.

After each animal was analyzed, the data for all the animals for each day were combined and there was obtained for each cell type the total number of cells present in all ears, the mean number of labeled cells per ear and the total number of labeled cells in all ears divided by the total number of cells present in all ears (percent labeled). Each segment was analyzed in a similar fashion and a record was made of the total number of cells per segment, the mean number of cells per segment the total number of labeled cells per segment, the mean number of labeled cells per segment divided by the total number of labeled cells in the cochleae (percent labeling activity per segment) and the number of labeled cells in a segment divided by the total number of cells in the segment (percent labeling per segment).

The posterior labyrinth was analyzed by counting the number of labeled cells for each cell type in every fourth section.

There were several indices used to measure the amount of labeling. The mean number of labeled cells for each cell type gave a measure of the amount of labeling which occurred. This parameter was useful for determining the time in development at which the greatest number of terminal mitoses of a given cell type occurred. There were large differences among the mean numbers of labeled cells of different types. These differences in the mean numbers of labeled cells could be attributed to the difference in the size of the cell populations, the DNA synthesis time (29) the cellular geometry (32) and other factors. In view of these differences other measures were used so that values for different cell types could be compared with one another. The first of these was called the "labeling activity" and was used to measure labeling on either a given day or in a segment. The total of all the means of the number of labeled cells for all the days or for all the cochleae within one day was the amount of labeling detectable by the methods used. The mean number of labeled cells which would occur per day or per segment was a fraction of this total. The fraction was called the labeling activity, was expressed as a percentage and was used in two ways. The first was, labeling activity per day

$$= \frac{\text{Mean number of labeled cells per day}}{\text{Total of mean number of labeled cells found on all days}} \times 100$$

The second was labeling activity per segment

$$= \frac{\text{Number of labeled cells per segment per day}}{\text{Total number of labeled cells per day}} \times 100$$

Another measure was called "percent labeled" and was available only for those eleven cell types in which counts of both labeled and unlabeled cells were made $\%\ \text{labeled} = \dfrac{\text{Number of labeled cells present per day}}{\text{Number of cells present per day}} \times 100$ The last index of labeling was a tabulation of the number of ears in which labeled cells of a given type were to be found At the beginning and the end of periods of terminal mitoses, not all ears would have labeled cells of the variety under study It was felt that results were more reliable when labeled cells were observed in all of the ears examined. This was especially important when there were low numbers of labeled cells observed

RESULTS

Cochlea

The cells of the cochlea may be classified into four groups according to the times during development at which terminal mitoses occurred. Many of the different classes of cells of the organ of Corti underwent most of their terminal mitoses on the 14th day of gestation. This was true for spiral ganglion cells, inner hair cells, outer hair cells, inner pillar cells, outer pillar cells, Deiter's cells, Hensen's cells, Claudius cells, inner supporting cells and external sulcus cells (Tables 4 5 and Figures 5 6 7 8)

The second pattern of terminal mitoses was to be found in epithelial cells of the limbus and internal sulcus cells (Fig 9) These two cell types underwent the greatest amount of their terminal mitoses on the 16th day of gestation

The cells of the stria vascularis, spiral ligament and Schwann cells of the spiral ganglion had most of their terminal mitoses on the first day post partum (Fig 10) All of these cell types still had cells undergoing terminal mitoses on the seventh day postpartum (Table 6)

The last group was characterized by a lack of a peak of terminal mitoses (Fig 11) This group consisted of cells of Reissner's membrane, epithelial cells of the basilar membrane and cells of the stroma of the limbus. The cells of Reissner's membrane underwent substantial amounts of terminal mitoses from the 13th day of gestation through the 3rd day postpartum. The epithelial cells of the basilar membrane and cells of the stroma of the limbus had similar patterns of terminal mitosis.

The spiral ganglion cells had a greater cumulative percent of labeling activity in the ears exposed on the 12th and 13th day of gestation than any other cell type in the cochlea (Table 7) This indicates that a greater proportion of the spiral ganglion cells undergo terminal mitosis before other cells in the organ of Corti.

The stria vascularis, spiral ligament Schwann cells, cells of Reissner's membrane epithelial cells of the basilar membrane cells of the limbus stroma all had terminal mitoses occurring as late as the 7th day postpartum (Table 6) The remaining 11 cell types did not have any terminal mitoses in the late postpartum period

Table 8 presents the number of labeled cells divided by the number of cells present for the 11 cell types for which counts of all cells were made The total of these labeling percentages was an indication of the amount of labeling which occurred with the radioautographic techniques and exposure times used in these experiments. There is a fourfold difference in the

TABLE 4 *Number of Fars with Labeled Cells Present—Cochlea*

	Day of Exposure to Tritiated Thymidine										
	Gestation							Postpartum Day			
Cell Type	10	12	13	14	15	10	18	1	3	5	7
Inner hair cells	0/4	3/5	4/8	8/8	4/6	2/6	1/6	0/3	0/2	0/2	0/3
Outer hair cells	0/4	3/5	8/8	8/8	6/6	5/6	0/6	0/3	0/2	0/2	0/3
Inner supporting cells	0/4	3/5	4/8	8/8	6/6	6/6	4/6	0/3	1/2	0/2	0/3
Deiter's cells	0/4	3/5	7/8	8/8	6/6	5/6	0/6	0/3	0/2	0/2	0/3
Inner Pillar cells	0/4	2/5	5/8	8/8	5/6	3/6	0/6	0/3	0/2	0/2	0/3
Outer Pillar cells	0/4	3/5	6/8	8/8	5/6	3/6	0/6	0/3	0/2	0/2	0/3
Claudius' cells	0/4	4/5	6/8	8/8	6/6	6/6	1/6	0/3	0/2	0/2	0/3
Hensen s cells	0/4	3/5	7/8	8/8	6/6	5/6	0/6	0/3	0/2	0/2	0/3
Spiral ganglion cells	0/4	2/5	6/8	8/8	6/6	2/6	0/6	0/3	0/2	0/2	0/3
I ternal Sulcus cells	0/4	1/5	4/8	8/8	6/6	6/6	4/6	0/3	0/2	0/2	0/3
External Sulcus cells	0/4	4/5	7/8	8/8	6/6	6/6	1/6	1/3	0/2	0/2	0/3
Reissner's membrane	0/4	2/5	6/8	8/8	6/6	6/6	0/6	3/3	2/2	2/2	3/3
Epithelium of Basilar membrane	0/4	1/5	4/8	8/8	6/6	6/6	6/6	3/3	2/2	0/2	1/3
Stria Vascularis	0/4	2/5	5/8	8/8	6/6	6/6	6/6	3/3	2/2	2/2	3/3
Spiral Ligament	0/4	0/5	4/8	8/8	6/6	6/6	6/6	3/3	2/2	2/2	3/3
Limbus Epithelium	0/4	1/5	2/8	8/8	6/6	6/6	6/6	0/3	1/2	0/2	0/3
Limbus Stroma	0/4	0/5	1/8	8/8	6/6	6/6	0/6	3/3	2/2	2/2	3/3
Schwann cells	0/4	2/5	4/8	8/8	6/6	6/6	6/6	3/3	2/2	2/2	3/3

Numerator – Number of ears with labeled cells.
Denominator – Number of ears observed.

cumulative percentage of labeling with spiral ganglion cells having the least, and external sulcus cells having the greatest cumulative percentage of labeling

The cochlear duct was divided into five equal segments from the base (0 0) to the apex (1 0) The labeling activity per segment for all 18 cell types is found in Table 0 and graphic representations of the outer hair cells, inner pillar cells and spiral ganglion cells are illustrated in Figures 12 13 and 14 The spatial distribution of labeling activity as a function of day of exposure to tritiated thymidine was examined Two factors were considered in evaluating the results. First if there were always a greater number of a given cell type in one segment, then the percentage of labeling activity for that segment could be high This was controlled in the 11 cell types in which total counts were done by comparing the percent labeled per segment with the labeling activity per segment (Table 9) There were no marked discrepancies between these two measures of the spatial distribution f the cell types within the adult cochlea. The interpretation of the

TABLE 5 *Mean Number of Labeled Cells per Day—Cochlea*

	Day of E pos re t Tritiated Thymidine											
	Gestation							Postpartum				Total of
Cell Type	10	12	13	14	15	16	18	1	3	5	7	Means
Inner hair cells	0	1.2	2.5	12.1	1	0 3	0.2	0	0	0	0	18.0
Outer hair cells	0	8 8	40 4	113.3	25.2	2.8	0	0	0	0	0	188.5
Inner supporting cells	0	2 0	8.0	46 4	12.3	1 .4	10 3	0	0.3	0	0	97.3
Deiter' cells	0	4 0	11.6	73.0	9.3	4.0	0	0	0	0	0	103 1
Inner Pillar cells	0	0.8	8 6	39.8	2.7	0.5	0	0	0	0	0	52 4
O ter Pillar cells	0	1 0	6 9	31 9	2.5	0.5	0	0	0	0	0	42 8
Claudius' cells	0	10 6	18 6	80 3	35 8	16.0	0.5	0	0	0	0	161.8
Hensen' cells	0	4.0	17.3	47 4	12.3	6.0	0	0	0	0	0	86 9
Spiral ganglion cells	0	17.8	83.4	120 6	22.0	0	0	0	0	0	0	244.3
Internal Sulcus cells	0	0.3	0 8	15 9	22.3	47.2	12.8	0	0	0	0	99 3
External Sulcus cells	0	4 2	19 9	45.4	29 7	23.8	0.2	0 1	0	0	0	123 3
Reissner' membrane	0	4 0	54 3	93.6	58 5	88 8	57 0	132.3	173.5	28.5	41 7	734.2
Epithelium of Basilar membrane	0	1 6	2 5	38 9	62.	90 7	1 3	89 0	27.0	0	0 7	384 4
Stria vascularis	0	2 6	9 0	96 1	93 6	89.0	39.5	770 0	438.5	93.0	45 0	1680.3
Spiral Ligament	0	0	7 1	101 9	216.5	2 9.2	577.0	2583 7	945.5	146.0	172.7	5032.7
Limbus Epithelium	0	0.2	1 1	47 4	92 8	157.3	22 7	0	2 5	0	0	324.0
Limbus Strom	0	0	0.3	15 3	72.	126 0	137 7	104.0	53.0	5 0	8.8	522.3
Schw nn cells	0	0 6	2 3	20 4	36.0	65 3	77.8	1172.3	986.0	172.0	128 3	2961 0

data for the remaining seven cell types must be based solely upon shifts in the labeling activity per segment

The second factor was the mean number of labeled cells observed in all of the cochlea within an exposure day. When the mean number of labeled cells was small then each cell had a large percentage of segmental labeling act ity associated with it. Therefore segmental distributions of labeling activ ty based on a small mean number of labeled cells should be inter pr ted with caution

Th ee neral patterns of terminal mitoses were noted with respect to p t n n th cochlea. The first group (Group I Table 9) consisted of the ll type n which cells located in the apical segment of the adult cochlea un l nt t rminal mitoses first, and those located in the basal segment ll dult cochlea underwent terminal mitoses last. This group consisted of nner hair cells, outer hair cells, inner pillar cells, outer pillar cells,

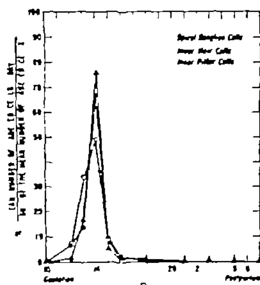


Fig. 5.

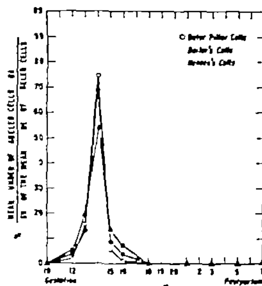


Fig. 6.

Fig. 5 Labeling acti ity of spiral g ngli n, inner hair and inner pillar cells. Days = D y f injection of tritiated thymidine

Fig. 6. Labeling activity f outer pillar Deiter and Hensen's cells Day = Day of injec tion f tritiated thymidi e.

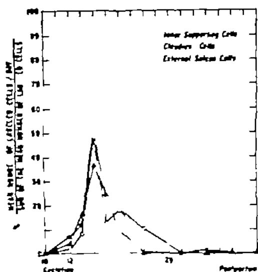


Fig. 7

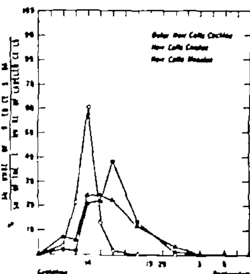


Fig. 8.

Fig. 7 Labeling activit f I ner upporti g, Claudi and external s lcu cells. Days = D y of i jecti n f triti ted thymidine

Fig. 8. Comparison f l beli g acti ity f outer hair cells of cochlea, hair cell of cristae nd hair cell f m cula D Day f i jection f tritiated thymidine

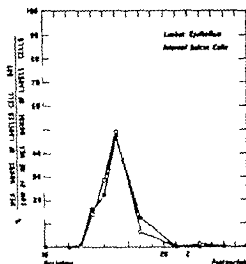


Fig. 9

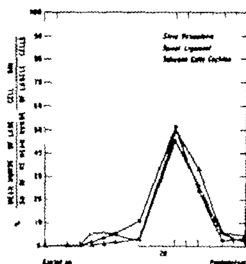


Fig. 10

Fig. 9 Labeling acti it f limbu epithel m nd internal lcu ll Da =Da of injection f tritiated thymidin

Fig. 10 Labell g acti ity f stri ascularis, piral ligament nd the Schwann cell f the cochlea. D ys = Day f i jection of tritiated thymidine

TABLE 6 *Cell Type Labeled on Postpartum Day 7*

Type	Mean Number of Labeled Cells Postpartum Day 7	% Labeling Activity Postpartum Day 7
Cochlea		
Reissner' membrane	41 7	5.7
Schwann cells		
Spiral ganglion	138 3	4.7
Spiral ligament	172.7	3 4
Stria ascularis	45.0	2 7
Limbus stroma	8.3	1 6
Epithelium		
Basilar membran	0	0.2
Posterior labyrinth		
Schwann cells		
Scarpa ganglion	92 0	10.2
Epithelial cells		
Cristae	3.0	2.6
Connecti tissue cells		
Cristae	8.6	2.3
ect tissue cells		
Maculae	13 1	2.0
Supporting cells		
Maculae	0 3	0 1

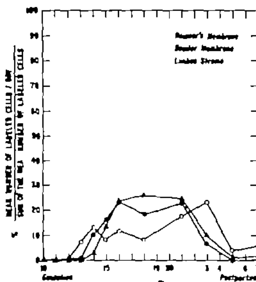


FIG 11 Labeling ctivity f th cell f R issner' me bra e, the epithelial cell f the basilar m mbran and th cell of th limbus troma Days – Day of injection f tritiated *thymidine*

Hensen s cells, Deiter's cells, and external sulcus cells (Figs. 12, 13) Three of the cell types followed a similar pattern of distribution except that there was a possible secondary shift to the apex among the youngest cells, i e., those cells which were labeled last The Claudius cells, inner supporting cells and internal sulcus cells make up this subgroup

The second group (Group II Table 9) consisted of the spiral ganglion cells, the Schwann cells, and the epithelial cells of the basilar membrane (Fig 14) The earliest labeled cells of this group i e., the oldest cells, were located in the basal segments. The terminal mitoses which occurred later in gestation or early neonatal life i e., the younger cells, were located in the apical segments

The last group (Group III Table 9) consists of cells of the spiral ligament, stria vascularis, epithelium of the limbus, limbus stroma and Reissner's membrane These five cell types did not have any apparent systematic distribution of labeled cells related to the time of exposure to the tritiated thymidine These were five of the seven cell types in which total cell numbers were not counted and the determination of the percent labeled per segment would be needed before a definitive statement could be made.

Posterior Labyrinth

The hair cells, supporting cells, epithelial cells and connective tissue cells of the three cristae were examined The cristae will be discussed together a the time and mean number of labeled cells in each class of cell was similar (Table 10 and Figs. 15 16 17 18) The labeling activity of the hair and supporting cells of the cristae followed a similar pattern

TABLE 7 *Cumulative Percent of Labeling Activity—Cochlea*

	Day of Exposure to Tritiated Thymidine										
	Gestation							Postpartum			
Cell Type	10	12	13	14	15	16	18	1	3	5	
Inner hair cells	0	6	20.6	87.8	97.2	95.9	100	100	100	100	100
Outer hair cells	0	3.6	23.0	85.1	96.5	100	100	100	100	100	100
Inner supporting cells	0	2.1	10.3	38.0	70.6	88.9	99.5	99.5	100	100	100
Deiter's cells	0	3.8	17	87.0	96.0	100	100	100	100	100	100
Inner pillar cells	0	1.3	[illegible]	93.9	99.1	100	100	100	100	100	100
Outer pillar cells	0	2.3	18.4	92.0	98.7	100	100	100	100	100	100
Claudius' cells	0	6.6	18.1	67	89.5	99	100	100	100	100	100
Hensen cell	0	4.6	24.5	79.0	93.0	100	100	100	100	100	100
Spiral ganglion cells	0	.2	41.3	90.6	99.6	100	100	100	100	100	100
Internal sulcus cells	0	0.3	1.1	1.1	59.8	87.1	100	100	100	100	100
External sulcus cells	0	3.4	19.5	56.3	60.4	99	99.9	100	100	100	100
Reissner' membrane	0	0.5	7.9	20.9	25.9	41.0	48.8	86.8	90.4	94.3	100
Epithelium of basilar membrane	0	0.4	1.1	11.2	27.5	31.1	69.6	92.8	99.8	99.8	100
Stria vascularis	0	0.2	0.7	6.5	12.2	[illegible]	19.9	[illegible]	91.8	[illegible]	100
Spiral ligament	0	0	0.1	2	6.3	12.0	23.5	[illegible]	83.6	96.5	100
Limbus epithelium	0	0.1	0.4	15.0	43.6	97.1	99.1	99.1	100	100	100
Limbus stroma	0	0	0.1	3.0	16.9	41.0	67.4	87.3	[illegible]	98.4	100
Schwann cells	0	0.1	0.1	0.8	2.0	3.9	6.5	56.2	89.5	93.3	100

(Fig. 19) There was very little labeling in the ears exposed on the 12th and 13th days of gestation. The labeling activity increased on the 14th day of gestation, reached a maximum on the 16th day of gestation, and continued into the postpartum period. The maximum on the 16th day of

TABLE 8 *Total Percent Labeled*

Cell Type	Total Percent Labeled for all Exposure Days
External sulcus cells	42.6
Outer hair cells	33.1
Inner pillar cells	33
Internal sulcus cells	32.4
Claudius cells	27.8
Inner supporting cells	26.6
Hensen cells	26.6
Outer pillar cells	25.4
Deiter' cells	24.4
Inner hair cells	12.6
Spiral ganglion cells	11.3

TABLE 9 *Segmental Labeling*

	Seg-ment	Day of Exposure t Tritiated Thymidine: Gestation 10	12	13	14	15	16	18	Postpartum 1	3	5	7
GROUP I					*Inner Hair Cells*							
~ Labeled	0.2	0	0	0	5.0	7 9	0	0	0	0	0	0
per segment	0 4	0	0.6	0.4	11.0	0 5	0	0	0	0	0	0
	0.6	0	0.5	1 0	16.5	0	0 9	0.5	0	0	0	0
	0.8	0	0 6	3 4	5 6	0	0	0	0	0	0	0
	1 0	0	1 4	3.5	0	0	0	0	0	0	0	0
~ Labeling	0.2	0	0	0	9.3	90 0	0	0	0	0	0	0
Activity	0 4	0	16 7	5.0	20.5	10 0	0	0	0	0	0	0
per segment	0.6	0	16 7	15.0	41 0	0	100	100	0	0	0	0
	0.8	0	16.7	35 0	12.0	0	0	0	0	0	0	0
	1.0	0	50 0	45 0	8.2	0	0	0	0	0	0	0
					Outer H ir Cells							
Labeled	0.2	0	0	1.2	19 0	14.5	3 6	0	0	0	0	0
per segment	0 4	0	0	3.5	38.1	0 0	0	0	0	0	0	0
	0.6	0	0 7	5.2	28.0	3 0	0	0	0	0	0	0
	0.8	0	1 1	10 4	19 1	2.9	0	0	0	0	0	0
	1.0	0	5.1	17 1	10 6	0 4	0	0	0	0	0	0
Labeling	0.2	0	0	2.4	12.9	31.3	100	0	0	0	0	0
Activity	0 4	0	0	9 7	31 7	40.8	0	0	0	0	0	0
per segment	0 6	0	14 7	17 9	30 7	13.0	0	0	0	0	0	0
	0 8	0	15.3	24 7	15 2	10.3		0	0	0	0	0
	1 0	0	70.0	45.3	9.5	1 6	0	0	0	0	0	0
					Inner Pillar Cells							
~ Labeled	0.2	0	0	0.	10.4	9 2	1.5	0	0	0	0	0
per segment	0 4	0	0	2.5	35 0	0.5	0	0	0	0	0	0
	0 6	0	0	3.9	29 1	0	0	0	0	0	0	0
	0.8	0	0.5	5.8	20.3	0 0	0	0	0	0	0	0
	1 0	0	1 7	10 2	9.2	0	0	0	0	0	0	0
Labeling	0.2	0	0	2.6	12.5	87.5	100	0	0	0	0	0
Activity	0 4	0	0	11.9	36.0	6 3	0	0	0	0	0	0
per segment	0 6	0	0	20.3	23.0	0	0	0	0	0	0	0
	0.8	0	25.0	22.3	15 1	6.3	0	0	0	0	0	0
	1 0	0	75 0	42.9	.5	0	0	0	0	0	0	0
					Outer P llar Cells							
Labeled	(2	0	0	0.5	14.2	9.5	1 7	0	0	0	0	0
per segment	0 4	0	0	1.8	30 8	0 1	0	0	0	0	0	0
	0 6	0	0		29.3	1 3	0	0	0	0	0	0
	(8		0 r	6 0	13.1	0	0	0	0	0	0	0
	1 0	0	1	6.8	8 3	0	0	0	0	0	0	0
Labeling	(2	(	0	1.8	13 3	81.3	100	0	0	0	0	0
Acti ity	4			9 8	32 2	5 3	0	0	0	0	0	0
per segment			(	29.5	33 3	13 3	(	0	0	0	0	0

Act of larγng 2°0

Table 9 *Cont*

	Segment	Gestation 10	1	13	14	13	16	18	Postpartum 1	3	3	
		Day of Exposure to Tritiated Th midine										
	0.8	0	20.0	23.5	12.8	0	0	0	0	0	0	0
	1 0	0	80.0	33 5	8 5	0	0	0	0	0	0	0
						Hensen Cells						
Labeled	0.2	0	0	0.5	14 1	6	3	0	0	0	0	0
per segment	0 4	0	0	2.	21	8 4	2.1	0	0	0	0	0
	0.6	0	0 6	4.2	10.0	3.2	0.3	0	0	0	0	0
	0.8	0	0	5.1	11 5	0.3	1.3	0	0	0	0	0
	1.0	0	5 0	11.6	4.5	0	0 9	0	0	0	0	0
Labeling	0.2	0	0	1 4	16.3	30 1	38 9	0	0	0	0	0
Acti ity	0 4	0	0	10 9	31.5	49 3	2 8	0	0	0	0	0
per segment	0 6	0	10 0	16.7	25 0	19.2	3 6	0	0	0	0	0
	0.8	0	0	20 4	13 9	1 4	18 7	0	0	0	0	0
	1 0	0	90 0	30.8	8 2	0	11 1	0	0	0	0	0
						Deiters' Cells						
Labeled	0 2	0	0	0 4	14 6	10 0	5 8	0	0	0	0	0
per segment	0 4	0	0	1 8	23 4	3.1	0	0	0	0	0	0
	0 6	0	0.3	1.2	19 1	1 1	0	0	0	0	0	0
	0 8	0	0	5 8	13 5	0 6	0	0	0	0	0	0
	1 0	0	5 0	8.5	9 9	0	0	0	0	0	0	0
Labeling	0 2	0	0	1 7	13 9	56 5	100	0	0	0	0	0
Acti ity	0 4	0	0	10 4	33.1	30 2	0	0	0	0	0	0
per segment	0 6	0	5 0	9 2	27 3	9 5	0	0	0	0	0	0
	0 8	0	0	25.9	15.1	3.8	0	0	0	0	0	0
	1 0	0	85.0	49	11 8	0	0	0	0	0	0	0
						External Sulcus Cells						
Labeled	0 2	0	2 9	0 2	9 1	10 6	15.9	0	0	0	0	0
per segment	0 4	0	0	1 3	15.4	9 4	4 5	0	0.3	0	0	0
	6	0	(3	2 2	22.8	13 4	6 4	0	0	0	0	0
	0 8		0	12 4	21 8	11 3	10 0	0 5	0	0	0	0
	1)	1	5 3	14 2	14 0	7 5	5 6	0	0	0	0	0
Labeling	2		36 1	0 6	13 8	19 0	40 4	0	0	0	0	0
Acti t	4			3 2	18	20 3	12.0	0	100	0	0	0
per segment			4 8	6 6	26 8	24 5	16 9	0	0	0	0	0
	8			48 9	21 5	22 2	1 1	100	0	0	0	0
	1		1	48	25 1	13 9	13.6	0	0	0	0	0
						Claudius Cells						
Label d			1	0 3	9 2	10	4.2	0	0	0	0	0
pe segme t	1		0 2	0 7	13.1	7.3	2.0	0	0	0	0	0
			0 2	2.0	18.3	4 9	1 8	0	0	0	0	0
	8	0	0	4.8	15 7	6.0	2.7	0.2	0	0	0	0
	1 0	0	6 8	7 9	12 9	4.3	2 0	0 3	0	0	0	0

TABLE 9 *Cont*

	Seg ment	Day f Exposure t Tritiated Thymidine Gestatio 10	12	13	14	15	16	18	Postpart m 1	3	5	7
% Labeling	0.2	0	0 4	1.3	10 8	21.3	28.3	0	0	0	0	0
Activity	0 4	0	3.4	5 4	20.2	29.2	18.5	0	0	0	0	0
per segment	0 0	0	1 9	14 0	28.2	16.1	14 6	0	0	0	0	0
	0 8	0	9 1	31 0	22.4	18.7	23.1	66 7	0	0	0	0
	1 0	0	85.3	48.3	18.3	11 7	18.4	33.3	0	0	0	0
					Inner Supporting Cell							
. Labeled	0.2	0	0.3	0 2	12.7	10 4	5.5	0 9	0	0	0	0
per segment	0 4	0	0	1 4	20 6	5 8	7 0	0 2	0	0 8	0	0
	0 6	0	0	2.2	18.0	1 7	0.3	1 4	0	0	0	0
	0 8	0	0	2.8	7.8	0.5	0.8	4.3	0	0	0	0
	1 0	0	1 9	3.2	7 0	1 1	1.3	5 7	0	0	0	0
" Labeling	0.2	0	10 0	1 6	15 0	41 1	19 6	4.8	0	0	0	0
Activity	0.4	0	0	14 1	32.8	38 6	37 0	1 6	0	100	0	0
per segment	0 6	0	0	21 7	29.8	10 8	33.1	11.3	0	0	0	0
	0.8	0	0	25.3	11 7	2.7	3 7	31 9	0	0	0	0
	1 0	0	90 0	31 4	10 7	6.8	6.5	50.3	0	0	0	0
					Internal Sulcus Cells							
Labeled	0.2	0	0	0	9 0	8 9	16.3	0	0	0	0	0
per segment	0.1	0	0	0.3	8.5	12.0	21 6	0.3	0	0	0	0
	0 6	0	0	0 4	7 1	11 6	17 0	2.1	0	0	0	0
	0 8	0	0	0 2	3 1	4.8	7 1	0	0	0	0	
	0 8	0	0	0.2	3.1	4.8	6.1	1	0	0	0	0
	1.0	0	0.3	0 4	0.1	2.2	4 6	11 6	0	0	0	0
Labeling	0.2	0	0	0	25 0	14.2	16.3	0	0	0	0	0
Activity	0.1	0	0	28 6	32.0	30 0	39.3	1.3	0	0	0	0
per segment	0 6	0	0	28.6	29 3	31 6	27 7	9 4	0	0	0	0
	0.8	0	0	11 3	12 0	12.2	9 6	29 9	0	0	0	0
	1 0	0	100 0	28 6	11 7	9.0	7 1	59.5	0	0	0	0
G ur II					*Spiral Ganglion Cells*							
Labeled	0 2	0	2.0	2.0	0	>0 1	0	0	0	0	0	0
per segment	0.1	0	1 0	7 6	0.2	0 1	0	0	0	0	0	0
	0.6	0	1 2	5	2.4	0.1	0 1	0	0	0	0	0
	0.8	0	0.3	1.3	15.2	0.5	0	0	0	0	0	0
	1 0	0	0 1	0.2	15.8	1 1	0 1	0	0	0	0	0
Labell g	0.2	0	11 9	10 6	0	0.8	0	0	0	0	0	0
Acti ity	0 1	0	22.5	5. 0	0.6	3.0	0	0	0	0	0	0
per segment	0 6	0	23 6	27.5	7 6	8 6	50.0	0	0	0	0	0
	0 8	(	6.	5 9	.0 1	9 5	0	0	0	0	0	0
	1 0	0	).2	1 0	41 7	78.0	50 0	0	0	0	0	0
					Schwann Cells							
Labeling	2	(	16 7	41 4	53 7	29 1	34 3	21	21.5	21.0	9 0	15 1
Acti it	1		(	5 6	20.5	30.7	30 1	25.5	22 0	21 0	11 9	25.1

1 I of I. B

TABLE 9 *Cont*

	Seg ment	Day of Exposure to Tritiated Thymidine: Gestation 10	12	13	14	15	16	18	Postpartum 1	3	5	7
per segment	0 6	0	0	33.9	5.8	15.9	22.7	21 6	22.6	19.2	10.2	15 5
	0.8	0	33.3	5.6	13 6	17 0	8.2	12.8	17 1	19 7	21 3	23.2
	1.0	0	0	5.8	6.4	7.2	4.8	12.9	13.0	16.0	44.5	21 1
						Epithelium of Basilar Membrane						
Labeling	0.2	0	0	0	53.8	31.0	23.6	7 0	13.5	0	0	0
Activity	0 4	0	0	45.0	25.9	43.1	36.6	23.8	9	3.7	0	0
per segment	0 6	0	0	20 0	16.2	18.0	21 7	11 0	12.3	3.7	0	0
	0 8	0	0	35.0	2.8	5.3	10 4	32.0	21.3	4 1	50 0	(
	1 0	0	0	0	1 6	2.	7	26.4	43.2	83.5	50 0	0
GROUP III						*Spiral ligament*						
Labeling	0.2	0	0	5.3	20 7	25.6	27.6	31 0	25.4	29.8	25 0	22.6
Activity	0.4	0	0	8.8	20.9	33.0	32 4	28.8	23 7	.3.3	23.3	33 8
per segment	0 6	0	0	7 0	21 8	20.8	23.4	19.2	18.0	14.5	19.5	22.2
	0.8	0	0	22.5	14.4	13.2	11.5	15 0	15.5	15.6	14.5	17.8
	1 0	0	0	56.5	22.5	7 4	5 2	8.1	11.3	11 8	12.8	3 7
						Stria vascularis						
Labelling	0.2	0	7 7	41 7	26.7	16.3	7 9	21 6	19.2	20.2	12.0	11 9
Activity	0.4	0	0	20.6	33.6	31.5	17.9	25.0	31 2	24 1	14.3	34.1
per segment	0.6	0	0	4 4	10.8	25.1	48.5	16 8	27.0	20 5	22.2	23 7
	0.8	0	0	18.1	11 6	12.1	19 0	11 6	16.8	18.4	25.9	15 6
	1 0	0	92.3	15.3	11 3	15 1	6.6	25.0	15 9	16.9	22.6	14.8
						Limbus Epithelium						
Labeling	0 2	0	0	11 1	27 4	18.7	19 3	0 7	0	0	0	0
Activity	0.4	0	0	11 1	32.4	25.6	23.8	1.5	0	0	0	0
per segment	0 6	0	0	11 1	21 1	32.3	35.6	4 4	0	0	0	0
	0.8	0	0	0	9 9	11.3	10 0	17.5	0	100	0	0
	1 0	0	100	66 7	9 2	12.0	8 8	5.9	0	0	0	0
						Limbus Stroma						
Labeling	0 2	0	0	60.0	41.0	25.3	25 7	21 4	16 3	27 4	20.0	12.0
Activity	0 4	0	0	40 0	29 7	23 8	37 4	24.2	17.2	19 8	40 0	4.0
per segment	0 6	0	0	0	16.2	35.1	24.6	27.5	18 1	1 7	20 0	30 0
	0 8	0	0	0	8 2	7.8	7 1	13 4	17 7	16 2	0	8 0
	1 0		0	0	4 9	3 0	8.2	13 5	30 6	18.9	20 0	40.0
						Reissner' Membrane						
Labelling	0 2		60 0	15.1	34.9	29 0	20.6	13.0	25.3	24.4	15.8	23.4
Activity	0 4		0	32.2	22.4	15 3	26 3	10 6	20 4	23 6	19.2	28.8
per segment	0		20.0	43.5	26.5	36.6	36 4	16.1	23 6	23 5	41 1	20.3
	)		0	8.3	8.4	14 8	8.1	18 4	9.3	13 1	15.4	10 0
	1		0	3.9	5.7	4 3	8 6	41 8	21 5	15.3	8.4	17 6

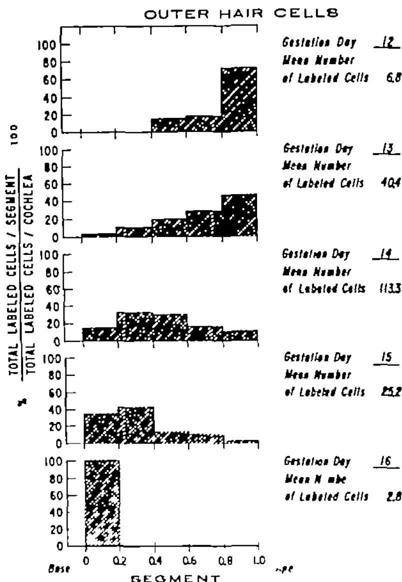


Fig. 12. Positi f labeled ter hai cells within the mature cochlea Gestation day I the day f I jection f the tritiated thymidine

gestation was 38 4 % labeling activity for the hair cells and 35 4 % labeling activity for the supporting cells. Both of these maxima were smaller than those noted for similar cell types in the cochlea

The connective tissue cells and the epithelial cells of the cristae had low percentages of labeling activity on the 14th and 15th days of gestation (Fig 10) The maximal percentage of labeling activity was found in the ears exposed on the first and third days postpartum Both of these cell types had terminal mitoses as late as the 7th day postpartum (Table 6) Their pattern f terminal mitosis was similar t that of the stria vascularis, spiral ligan nt and Schwann cells.

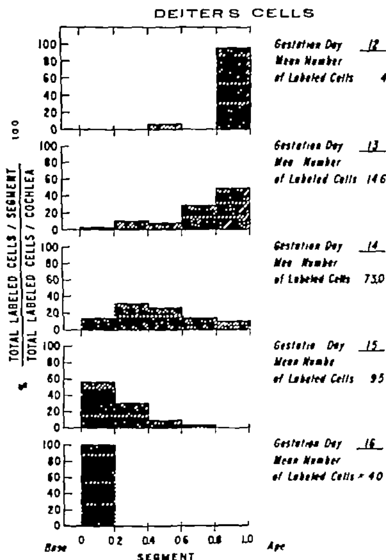


FIG. 12. Position f labeled Deiter's cell withi the mature cochlea. Gestation day is the day of injection of the tritiated thymidine.

The mean number of terminal mitoses of the two maculae were similar with one exception (Table 10 and Figs. 20, 21) The mean number of labeled connective tissue cells (Fig 22) in the macula of the saccule was much greater than the mean number found in the macula of the utricle

Figure 23 illustrates the combined percent labeling activity of the cell types in the two maculae. The hair cells and supporting cells follow a similar pattern of terminal mitosis. The percent of labeling activity was between 5 and 10% in the ears exposed on the 12th and 13th day of gestation. There was an increase in labeling activity for both cell types in the ears exposed on the 14th, 15th and 16th days of gestation. The percent of

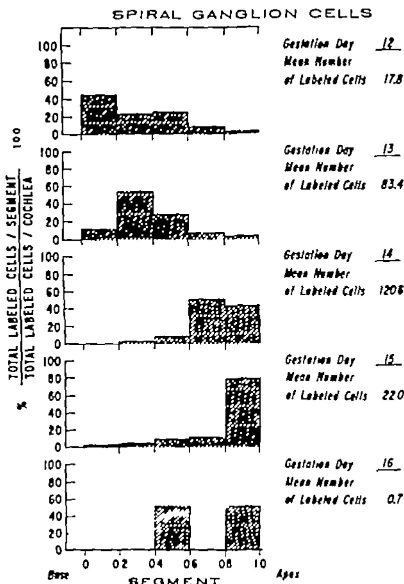


Fig. 14 Position f labeled spiral ganglion cell withi the mat re cochlea Gest tion d y i the day f injectio f the tritiated thymidine

labeling activity never exceeded 25% per day of exposure for either the hair or supporting cells of the maculae. The labeling activity persisted until the fifth day postpartum for the hair cells and until the seventh day post partum for the supporting cells.

The pattern of labeling activity (Table 10 and Fig 23) for the connective tissue cells of the two maculae was similar to that of the cristae in that the maximum percent of labeling activity was noted on the first and third days postpartum The terminal mitoses of the connective tissue cells of the two maculae continued until the seventh day postpartum

The labeling activity of the ganglion cells and Schwann cells of Scarpa s

TABLE 10. *Number of Ears with Labeled Cells Present—Posterior Labyrinth*

	Day of Exposure to Tritiated Thymidine										
	Gestation							Postpartum			
Cell Type	10	12	13	14	15	16	18	1	3	5	7
Horizontal crista											
Hair cells	0/4	2/5	3/8	8/8	6/6	6/6	6/6	0/3	0/2	0/2	0/3
Supporting cells	0/4	2/5	1/8	8/8	6/6	6/6	6/6	0/3	0/2	0/2	0/3
Connective tissue	0/4	1/5	0/8	7/8	6/6	6/6	6/6	3/3	2/2	2/2	3/3
Epithelial cells	0/4	0/5	1/8	3/8	3/6	4/6	6/6	3/3	2/2	2/2	1/3
Anterior crista											
Hair cells	0/4	2/5	4/8	8/8	6/6	6/6	6/6	2/3	0/2	0/2	0/3
Supporting cells	0/4	2/5	5/8	8/8	6/6	6/6	6/6	2/3	0/2	0/2	0/3
Connective tissue	0/4	0/5	4/8	6/8	6/6	6/6	6/6	3/3	2/2	2/2	2/3
Epithelial cells	0/4	0/5	0/8	5/8	6/6	6/6	4/6	3/3	2/2	1/2	2/3
Posterior crista											
Hair cells	0/4	2/5	1/8	8/8	6/6	6/6	6/6	1/3	0/2	0/2	0/3
Supporting cells	0/4	1/5	6/8	/8	5/6	6/6	6/6	2/3	1/2	0/2	0/3
Connective tissue	0/4	1/5	0/8	7/8	6/6	6/6	6/6	3/3	2/2	1/2	3/3
Epithelial cells	0/4	0/5	1/8	3/8	2/6	6/6	4/6	3/3	2/2	1/2	1/3
Utricle macula											
Hair cells	0/4	2/5	6/8	8/8	6/6	6/6	6/6	3/3	0/2	0/2	0/3
Supporting cells	0/4	2/5	4/8	8/8	6/6	6/6	6/6	3/3	1/2	0/2	0/3
Connective tissue	0/4	0/5	0/8	6/8	6/6	6/6	6/6	3/3	2/2	1/2	3/3
Saccule macula											
Hair cells	0/4	3/5	6/8	8/8	6/6	6/6	6/6	3/3	2/2	1/2	0/3
Supporting cells	0/4	3/5	7/8	8/8	6/6	6/6	6/6	3/3	2/2	1/2	1/3
Connective tissue	0/4	0/5	1/8	7/8	6/6	6/6	6/6	3/3	2/2	1/2	3/3
Scarpa ganglion											
Ganglion cells	0/4	4/5	1/8	1/8	1/6	0/6	1/6	0/3	0/2	0/2	0/3
Schwann cells	0/4	2/5	5/8	8/8	6/6	6/6	6/6	3/3	2/2	2/2	3/3

Numerator = Number of ears with labeled cells.
Denominator = Number of ears observed.

ganglion is illustrated in Figure 24 The Scarpa s ganglion cells underwent 90 7% of their labeling activity on the 12th day of gestation. Labeled ganglion cells occurred in 4 of the 5 ears exposed on the 12th day of gesta tion (Table 10) During the 13th day of gestation 6.2% of labeling activity occurred in one of eight ears. An occasional labeled Scarpa s ganglion cells was seen on the 14th, 15th and 18th day of gestation The Schwann cells of Scarpa s ganglion had a low but gradually increasing percentage of label ing activity until the day of birth when 33.8% of the labeling activity was found (Fig 24) On the third day postpartum 34.5% labeling activity was observed and 10 2% of the terminal mitoses of the Schwann cells were noted on the th day postpartum.

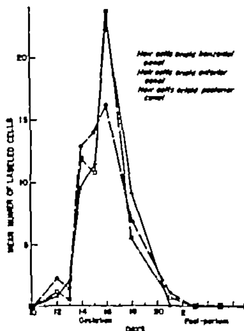


Fig 15

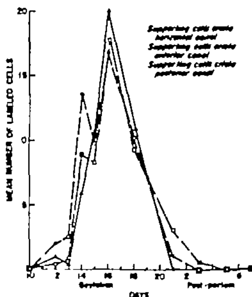


Fig 10

Fig. 15 Mea n mber of l beled hair cell in th three crist D ys = D y of l jectl f tritl ted thymidine

Fig. 16. Mea n mber f l beled supporting ell in the three crista D ys = Day of injection of tritiated thymidi

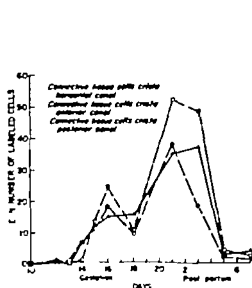


Fig 17

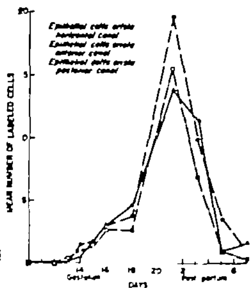


Fig 18

Fig. 17 M mber of l beled connecti ti cell l th thre cri t D ys = D y of l jection f tritiated th midine

Fig. 18. Mea mbe f l beled pith li l cell l the three cri t D ys = Day f l jecti n of triti ted l m d

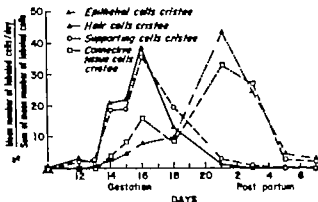


FIG. 19 Labell g activity f the hai supporti g, co necti ti nd epith li l cell of the three cri ta Days – Day f i jecti f triti ted thymidi

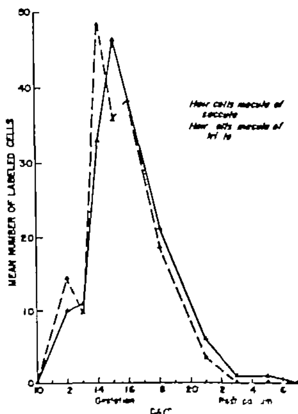


FIG. 20 Mea number of l beled h i cell f the two maculae D y – Day of i jection f tritiated thymidi

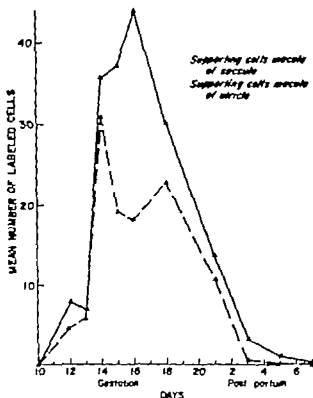


FIG. 21 Mean number of labeled supporting cells of the tw maculae D ys = D y of I jection of tritiated thymidine

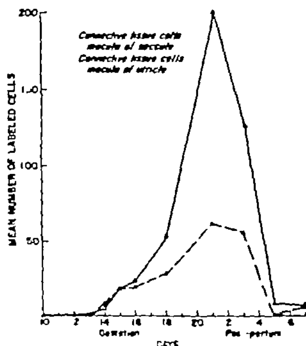


FIG. 22. M n n mber l labeled ecti t u cell of the tw macula Days = Da of injection of trit ted thym d

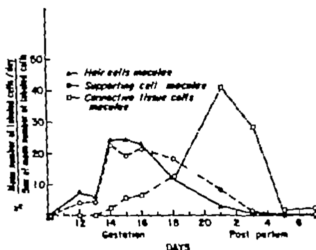


FIG. 22. Labelling acti ity of th hair supporting nd connecti tissue cell of the two macula D ys = D y of i jection of triti ted thymidine.

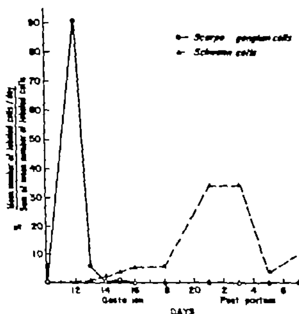


FIG. 21. Labelling activity f the Scarpa's ganglion and Schwa n cell of Scarpa's ganglion. D ys = D y f i jection f tritiated thymidin

DISCUSSION

No terminal mitoses were detected in the ears exposed to tri midine on the 10th day of gestation. Previous work (56) has s there is transplacental spread of tritiated thymidine as early as day of gestation. However the possibility that there was not any tritiated thymidine on the tenth day of gestation was investig CBA-J mice, in their tenth day of pregnancy were injected intr ally with the standard dose of tritiated thymidine They were one hour after injection and the embryos prepared for radioau The resultant radioautographs of the ten-day old embryos show labeling in the otic vesicle It is probable that cells labeled on the of gestation underwent so many cellular divisions that there wa detectable when the ears were examined 24 days later on the postpartum

The abscissae of the graphs in the preceding pages were in do time intervals were not constant in that each day was exami gestation day 12 to gestation day 16 but there were either two or intervals between the data points for the other days. In some inst number of labeled cells would have been much greater if days been omitted from the experimental design This would result in r of the percent of labeling activity on a given day The large m percent labeling activity found for the cells of the cochlea in exposed to tritiated thymidine on the 14th day of gestation woul greatly affected as there were very few labeled cells observed when every other or every third day was sampled The greatest eff be in those cells, e.g the hair cells of the maculae cristae etc., there were a large number of labeled cells observed at the tim when every second or every third day was sampled The curve f cells would be lower

Eleven cell types (Table 6) were noted to have terminal mitos seventh day postpartum It was possible that some of these c continued to undergo mitoses during adult life If there were many cell types undergoing continual mitosis, then the percent of labelin would be lower because further cell divisions would dilute the acute studies with tritiated thymidine in adult animals Koburg (evidence of a low level of mitotic activity in the cells of the spiral stria vascularis, epithelium of the basilar membrane epitheliu limbus, stroma of the limbus, and Reissner's membrane These all in the group of the eleven cell types which still showed termin

on the seventh day postpartum (Table 6) The number of cells involved in these mitoses occurring in the mature cochlea was small and this should not substantially affect the pattern of terminal mitosis which was obtained in the present study

The time during which the labeled thymidine was available to the dividing cells was assumed to be one hour after injection (9, 10 22, 29 30, 34 46) The cells which remained labeled in the mature labyrinth were those which were in the DNA synthetic phase during the hour in which the tritiated thymidine was available Previous workers (22) have estimated that if a cell undergoes three or four additional divisions after exposure to tritiated thymidine then the label will be so diluted as to be undetected by the conventional radioautographic techniques. It would appear that those cells which remained labeled in the mature labyrinth had undergone no more than 3 or 4 terminal mitoses. The heavily labeled cells had, at the most, undergone one division after the uptake of tritiated thymidine Some of the labeled cells found in the labyrinth exposed on the 12th day of gestation (Fig 2 A) were lightly labeled and probably represent second, third and fourth cellular divisions. The labeled cells seen in the ears exposed in the postpartum period were heavily labeled, and this was probably due to a greater concentration of tritiated thymidine available to the inner ear and to the cessation of cell division.

A general observation was that the amount of label per cell was greater in those ears which were exposed to tritiated thymidine during the end of the period of terminal mitosis. For example, the apical hair cells of the cochlea on the 12th day of gestation had fewer grains per nucleus than those found in the basal turn of the cochlea labeled on the 16th day of gestation (Fig 2 A, 2 B) The time of cessation of cell division for a given cell type was determined more accurately than the time of the beginning of the period of terminal mitoses, because of the ability to detect the third and fourth cell divisions. A difference in the number of grains per nucleus between different cell types was noted (Figs. 1 2, 3) which may be accounted for by the physical difference in the cells (32) and by differences in the duration of the DNA synthetic phase (29)

There was a difference in the time of terminal mitoses for the hair and supporting cells of the cochlea and those of the posterior labyrinth (Fig 8) The hair and supporting cells of the cochlea underwent terminal mitoses before those of the posterior labyrinth. The temporal pattern of terminal mitoses in the cochlea also differed (Figs. 5 6, 7 8, 9) There were sharp peaks of terminal mitoses in the cells of the organ of Corti in animals exposed to label on the 14th and 16th days of gestation The hair and supporting cells of the posterior labyrinth underwent the bulk of their terminal mitoses over a five day period from the 14th to the 18th day of gestation and were characterized by comparatively modest maxima of labelling activity the hair and supporting cells of the maculae had smaller maxima than those of the cristae (Figs. 8, 19 23) This different time

pattern of terminal mitoses may make the organ of Corti more susceptible to an embryological insult at a given time than the vestibular apparatus. Several types of embryological insults occurring on the 14th day of gestation could interfere with cellular division This would damage almost the entire organ of Corti but have little effect on the vestibular apparatus. This difference in terminal mitoses of the two portions of the membranous labyrinth may have its clinical expression in the large numbers of congenitally deaf patients who have normal or near normal vestibular responses (44)

There were similarities in the pattern of terminal mitoses between the cochlea and the vestibular apparatus The ganglion cells of Scarpa s ganglion underwent their terminal mitoses before the other portions of the vestibular apparatus (Figs. 19 23 24) The spiral ganglion cells showed a similar tendency to be the earliest group of cells to undergo terminal mitoses within the cochlea (Table 7) It would appear that the ganglion cells of the eighth nerve were the first cells to undergo terminal mitosis and consequently become the oldest cells of the inner ear The data indicate that the ganglion cells of Scarpa s ganglion undergo terminal mitosis before those of the spiral ganglion This observation is in agreement with Streeter's (53) finding that in man the cells of the Scarpa s ganglion were identifiable somewhat earlier than those of the spiral ganglion

Most studies (5 8 41 57 58) have shown that the cytological maturation of the organ of Corti begins at the basal end and proceeds to the apex. Bélanger s (6) study is an exception to these other reports. The position of the cells in the mature organ of Corti which underwent their terminal mitoses at different times, in part presents a different pattern of development The cells of the organ of Corti that is, the hair cells, the pillar cells and Deiter s cells, were distributed in such a way that the oldest cells, the cells which undergo terminal mitoses first were at the apex and the youngest cells, the cells which undergo terminal mitoses last were at the base The apical cells wait longer after they have undergone terminal mitoses before they reach their mature form than do the hair cells located in the basal turn (Figs. 12, 13)

The observation that the spiral ganglion cells underwent their terminal mitoses starting at the base and ending at the apex (Fig 14) suggests that the spiral ganglion cells could be responsible for inducing the morphological changes within the organ of Corti Tello (54) has noted in the mouse by means of silver stains, that portions of the afferent fibers of the cochlea innervate the hair cells beginning at the basal turn It takes several days *for the afferent* innervation to reach the apex. The afferent innervation of the hair cells could play a role in initiating the differentiation of the cells of the organ of Corti.

Rossi (43) has studied the pattern of innervation of the efferent fibers in the guinea pig with the acetylcholinesterase stains. The efferent fibers also innervate the base first and proceed to the apex The electron microscopic observations of Kikuchi and Hilding (24) in the Shaker 1 mouse

demonstrate that identifiable efferent innervation does not occur in the shaker 1 until the 14th day postpartum, which is several days after the cochlea has achieved its cytological differentiation It would appear from these observations that the efferents could not be primarily responsible for the cellular differentiation of the organ of Corti although they may be involved in the formation of the spaces of Nuel

Another point to be considered is what aspect of cytological differentiation is being studied The work of Wada (57) and Weibal (58) was based on light microscopy They described the details of cellular development and the dimensions of the developing cochlear duct. Kikuchi and Hilding (23) and Kimura (25) have shown with the electron microscope that cytological differentiation of the hair cells occurs early in the mouse They reported that the kinocilia of the hair cells were apparent at the first day post partum There is no information concerning the topographical appearance or disappearance of the kinocilia in the cochlea and this aspect of differentiation would be of great interest. The histochemical correlates of cellular differentiation should also be considered in establishing the topographical pattern of differentiation Some aspects of this have been described by Titova (55) and Milaire (37)

The observation that the oldest cells of the organ of Corti appear at the apex and the youngest at the base suggests a hypothesis concerning the growth of the cochlear duct. In the twelve day mouse embryo the cochlear duct is a small out-pocketing from the region of the otic vesicle which will eventually become the saccule (58) This small appendix grows and spirals until the mature form of the cochlea is obtained The observations that the older hair cells were at the apex would suggest that the growth area might be at the junction of the cochlear duct and the primitive saccule. Growth by cell division at this point would cause the apex, with its already divided cells, to move away from the saccule The spiral ganglion cells appear not to take part in this growth pattern but follow their own pattern so that the oldest spiral ganglion cells deploy themselves at the basal portion of the modiolus and the youngest at the apical portion In the mature cochlea the oldest cells of the organ of Corti are nearest the youngest cells of the spiral ganglion, and vice versa.

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DEVELOPMENT OF THE INNER EAR OF THE MOUSE A RADIOAUTOGRAPHIC STUDY OF TERMINAL MITOSES

R. J RUBEN

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SUPPLEMENTUM 220

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Dedicated to Stacy Rufus Guild
Anatomist & Teacher 1890–1966

The development of the inner ear of vertebrates has been examined in various ways. During the 19th and early 20th centuries Boettcher (8) Retzius (41) Held (21) and others studied the morphological development of the membranous labyrinth. More recently Bast and Anson (5) have made major contributions to the understanding of the morphological development of the ear There have been two detailed morphological studies on the development of the inner ear of the rodent (57 58) All of these studies have demonstrated that cytological differentiation appears first at the base of the cochlea and proceeds to the apex over several days.

Ramón y Cajal (40) and Tello (54) have examined the pattern of afferent innervation of the developing inner ear of the mouse. Tello observed that some of the afferent fibers innervated the basal turn before the apex. Rossi (43) studied the pattern of efferent innervation and noted that the efferent fibers to the cochlea began their innervation at the base

Experimental manipulation of the developing inner ear has long been practiced by embryologists and this work has been reviewed by Benoit (7) Among many sources of influence which contribute to the development of the inner ear are the mesenchymal and neural tissues which serves as successive inducers of the inner ear (59) There has been recent work on the histochemical differentiation of the inner ear (37 55) Kikuchi and Hilding (23) have examined the ultrastructure of the later stages of th development of the inner ear of the mouse Studies of the development of the various electrical potentials of the ear have been carried out (1 2, 28 35 36, 47) and have demonstrated that the appearance of the electrophysiological responses are correlated with the cytological differentiation of the cochlea.

Genetic anomalies have been used to study the processes involved in the normal development of the inner ear The work of Deol (11 12, 13) demonstrates that anomalies of the neural tube are associated with vari malformations of the inner ear Kikuchi's and Hilding's (24) obser at of a deficiency of efferent innervation in the shaker 1 mutant mou suggests an interrelationship between the development of the brai and the inner ear Ross (42) has noted central nervous system defic in genetically deaf mice

The studies in this report deal with the terminal mitoses of the the membranous labyrinth by analyzing radioautographs of th following labeling with tritiated thymidine during development mitoses in this study are considered to be the last divisions undergoes. The terminal mitoses serve as an index of times of ment of a permanent cell population. Cell division ceases for

of cells in the inner ear of the mouse during gestation or soon after birth (26). The labeled cells in the adult ear represent the terminal mitoses which occurred at the time during development when the ear was exposed to tritiated thymidine. The information obtained from the knowledge of the temporal and spatial patterns of terminal mitoses should be useful for the further understanding of normal and abnormal development of the membranous labyrinth.

There are many reports in which this technique has been used to study the developmental pattern of terminal mitoses in other organs (3, 10, 22, 29, 30, 33, 34, 49, 56). There is one study on the incorporation of tritiated thymidine into the ear of adult animals (26), but there are, to my knowledge, no reports of tritiated thymidine radioautographic detection of terminal mitoses in the inner ear during prenatal development and early postnatal life. The mouse was chosen as an experimental animal because of the large number of different strains of genetically deaf mice (51).

The present work seeks to map, in time and space, the terminal mitoses of the different cell types of the membranous labyrinth, by means of labeling with tritiated thymidine. The theoretical and technical aspects of this technique are reported elsewhere (9, 10, 14, 15, 22, 30, 31, 32, 33, 34, 39, 46). Thymidine is incorporated into the DNA of a cell during the synthetic phase of the mitotic cycle and remains as part of the DNA of the two daughter cells. The thymidine is available to cells in the mouse for about one hour after injection (9, 10, 22, 29, 30, 34, 46). If the thymidine is labeled with a radioactive molecule such as tritium, then the DNA which incorporates the labeled thymidine can be located within the cell nucleus. All of the cells which are synthesizing DNA at the time when the tritiated thymidine is available will become labeled and divide. Some of the labeled cells will divide only once and will have a maximum amount of labeled DNA, whereas others will continue to divide and dilute the label.

After several days the animals, which were exposed to tritiated thymidine, are sacrificed. Radioautographs are then made by covering the tissue with a photographic emulsion, which will be exposed by the beta particles emitted from the tritium. Those cells in which labeled nuclei are detected by the radioautographs are the daughter or granddaughter cells of the cells which were in their synthetic phase during the period of exposure to the tritiated thymidine. These labeled cells, in the inner ear, have undergone their terminal mitoses soon after the time they were exposed to the tritiated thymidine. The cells without label, or in which the label is undetectable, represent those which did not incorporate the tritiated thymidine or went on to have many cell divisions after their exposure to the tritiated thymidine. The times when the various cell types undergo their terminal mitoses can be established by exposing a series of animals to tritiated thymidine at different times during gestation.

PROCEDURE

I *Experimental Design*

Fourteen pregnant CBA J mice (supplied from the Jackson Laboratory Bar Harbor Maine) under one year of age were each injected intraperitoneally with 0 6 μ c of tritiated thymidine per gram of body weight The tritiated thymidine (Schwarz BioResearch, Inc.) had a specific activity of 3 curies per millimole and a concentration of 0.5 millicuries per ml In addition, five litters of CBA-J mice were injected subcutaneously with the same dosage of tritiated thymidine on different days after birth. The day of gestation was determined by the vaginal plug method The day when the plug was observed was called gestation day 1 and the day of birth was called postpartum day 1 Fourteen of the nineteen litters had a gestation period of 20 days and five had a gestation period of 21 days. The animals were exposed to tritiated thymidine at a time between 0.30 a.m and 12 30 p.m on the 10th 12th, 13th, 14th, 15th 16th or 18th day of gestation and on the 1st, 3rd, 5th or 7th day postpartum. The ears of all these animals grew to anatomical maturity before they were sacrificed for examination

Fifty-three inner ears from the litters were analyzed. Table 1 shows the number of ears examined for each day on which tritiated thymidine was administered. Ears from two different litters were examined for all days from the 10th day of gestation until the first day postpartum Only one litter per day was used for the observations on postpartum days 3, 5 and 7 The ears were identified according to litter and the ears from an individual within a litter were not separately marked The animals were sacrificed from the 13th to the 22nd day postpartum, the greatest number being sacrificed on the 15th day postpartum.

II *Tissue Processing*

The animals were anesthetized in a chloroform bottle (45) The thorax was opened and a No 25 gauge needle was placed in the left ventricle The animals were perfused with 10 ml of a balanced salt solution and then with an additional 10 ml of 10% Acrolein buffered with phosphate to pH 7 4 (50) The head was severed, the skin removed and the bullae and calvarium opened. The specimen was placed in the 10% Acrolein solution and kept in the refrigerator at 4 C for 24 hours. After that it was washed in tap water for one half hour and the specimen was decalcified over a three day period by a 10% solution of disodium ethylenediaminetetraacetate (EDTA) with 2.5 or 5.0% polyvinylpyrrolidone (PVP) and buffered to

TABLE 1 *Number of Ears Exposed to Tritiated Thymidine and Length of Exposure of Emulsion*

Time of Exposure To Tritiated Thymidine	Weeks of Exposure of Emulsion					Total Number of Ears per Day
	2	4	6	9	11	
Gestation Day						
10	1	1	1	1		4
12		2	1	2		5
13	1	1	2	3	1	8
14	1	1	2	3	1	8
15	1	1	2	2		6
16	1	1	2	1	1	6
18	1	1	2	2		6
Postpartum Day						
1	1		1	1		3
3			1	1		2
5			1	1		2
7			2	1		3
			Total Number of Ears in Study = 53			

pH 7.4 with a Tris hydroxymethyl aminomethane buffer (4, 17, 20, 38). The specimen was again washed in tap water for one half hour. Dehydration was accomplished by placing the specimens for 48 hours in a 1:1 (v/v) solution of ethylene glycol monomethyl ether and methyl alcohol (50). They were placed in 2% celloidin dissolved in the 1:1 ethylene glycol monomethyl ether and methyl alcohol for 24 hours. This was followed by hardening in chloroform for 12 hours. They were then placed in 90% polyethylene glycol 400-distearate and 10% cetyl alcohol (w/w) at 37 C for 72 hours (50, 52). The tissue was embedded in the polyethylene glycol 400-distearate and cetyl alcohol and was placed in the refrigerator until sectioning.

III *Radioautographic Technique*

The ears were sectioned at 10 μ in a plane approximately parallel to the axis of the cochlea. After serially mounting the sections in a 0.1% (w/w) gelatin solution, the polyethylene glycol and cetyl alcohol were removed with xylene and the sections were hydrated. They were then dipped in a solution of one part Kodak NTB-2 emulsion and one part distilled water (v/v) at 40 C, dried for 20 minutes in a humid oven at 30 C and stored in light proof boxes for three to eleven weeks in dry ice. The length of time of exposure made some difference in the number of labeled cells detected but this was small when compared to the variation between litter mates or different litters injected on the same day with the same duration of exposure of the emulsion.

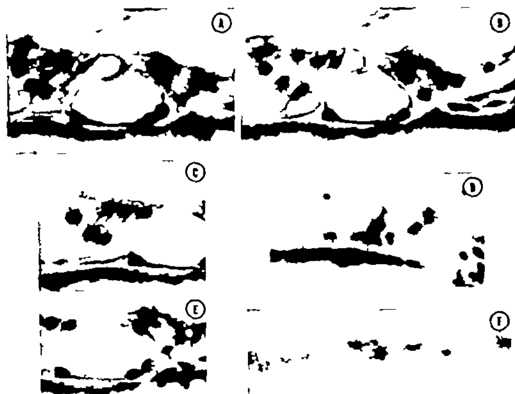


FIG. 1 Radioa tographs 830 ( ) Ear exposed t tritiated thymidine the 14th day f gest tion. Labeled outer hair cells, Deiter's cell, internal supporting cells. (*b*) Ear exposed t tritiated thymidine on the 14th day of gestation. Labeled Hensen cell, outer hai cell, Deiter's cell, inner hair cell, internal s pporting cells. ( ) Ea exposed t tritiated thymidine the 14th day f gestation. Labeled Hensen cell, Deiter' cell and outer hai cell. (*d*) Ear exposed t tritiated thymidine on the 14th day of gestation. Labeled Cl udius' cell. ( ) Ear xposed t tritiated thymidine on the 14th day f gestation Labeled inner pill cell. (*f*) Ear exposed t tritiated thymidine on the first day postpartum. Labeled cell in R issner' membrane.

After exposure the slides were developed in Kodak Dektol developer fixed with hypo, washed in distilled water and stained with toluidine blue Examples of the radioautographs are illustrated in Figures 1 2 and 3

IV *Methods of Observation*

Every fourth section was examined Eighteen cell types were studied in the cochlea and 20 cell types were studied in the vestibular apparatus (Table 2) The cochleae were reconstructed using the methods of Guild and Schuknecht (18 19 48) This method projects the turns of the cochlear spiral onto a common plane perpendicular to the axis of the cochlea. A modification was made in order to incorporate cells further from the modiolus than the outer hair cells. The modification was that the tangent of the external sulcus cells was used instead of the tangent of the outer

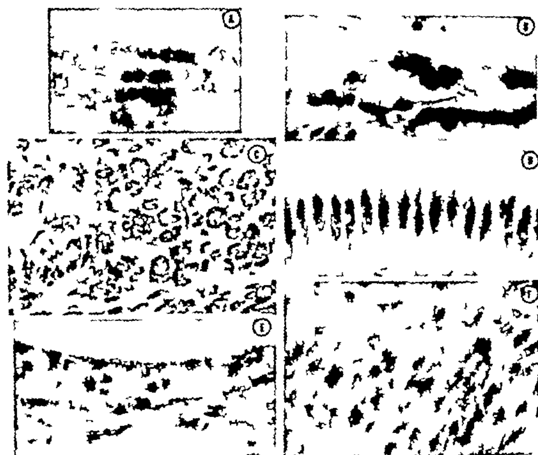


FIG. 2. Il dioautograpl s. ×330. (a) Ea xposed t triti ted thymidin n the 12th day f gest ti n. Labeled at hai cell piral turn (b) Ear xposed t tritiated thymidin n the 16th da of gest tion Labeled uter hai cell Deit r' cell and epithelial cell f basila membr ne t the basal turn ( ) Ear xposed t t iti ted th midin on the 14th da f gestati n Labeled piral gangli n cell (d) Ea exposed t tritiated th midn n the 16th day of gestati n. Labeled cell f th epith lium f the limbu ( ) Ea xposed t t iti ted th midine n the first da postpartum Labeled cell f the tria v scular nd th pi l ligament (f) Ea exposed t t iti ted thymidine on the first d post partum. Labeled cell f the piral lig ment

hair cells t determine the radius of each turn An individual reconstruc tion was made for each cochlea based on the tangents of the external sulcus cells Nine co ies f this reco nstruction were made and the 18 cell types were pl tted in pairs on these reconstructions Figure 4 represents the reco nstructi n f r animal no 2044b-1 f the inner and outer hair cells One to five bservati ns were made from each section depending upon the number f tim s the cochlear spiral was intersected by the plane of the section (Fig. 4 If the secti n was near the m diolus, i.e., mid modiolar as many s f s p ral bservati ns could be made as five different portio n f th cochlear duct were bserved in the section (e.g Fig. 4 section n) If th secti n was taken at so me distance from the modiolus

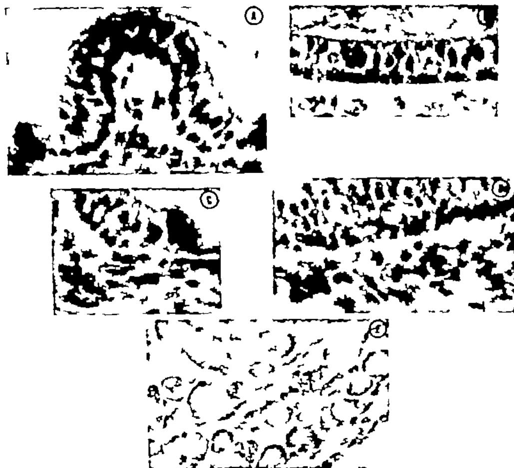


FIG. 3 Radioautographs. 830. ( ) Ear exposed t tritiated thymidine on the 18th day f gest tl Labeled hair nd supporting cells of the crista of the terior semicircular canal (b) Ear exposed t tritiated thymidine on the 18th d y of gestation. Labeled hair and pporting cell f the macula of the saccul ( ) Ear xposed t tritiated thymidi e on the f rst day postpartum. Labeled epithelial and connectiv tissu cell f the crist of the nterior semi-circular canal. (d) Ear xposed t tritiated thymidi on the first day postpartum. Labeled connectiv tissue cell f the macula of the utricl ( ) Ear posed to tritiated thymidin on the 12th day f gestation Labeled Scarpa's ganglion cells.

(e.g Fig 4 section no 10) then only one observation was made because the section cut through only one portion of the cochlear duct At each observation point the total number of cells in each class and the number of labeled cells in each class (or in some instances, only the number of labeled cells) was recorded If the cell type in question was *not present* at the observation point, a zero was recorded. For example in Figure 4 zeros are found at section no 10 since the inner and outer hair cells were not present

The total number of cells, and the number of labeled cells at each ob-

TABLE 2 *Cell Types Examined*

Cochlea
- Inner hair cells
- Outer hair cells
- Inner supporting cells of inner hair cells
- Deiters' cells
- Inner pillar cells
- Outer pillar cells
- Claudius cells
- Hensen's cells
- Internal sulcus cells
- External sulcus cells
- Reissner's membrane
- Epithelium of basila membran
- Stria vascularis
- Spiral ligament
- Limbus epithell m
- Limbus stroma
- Spiral ganglion cells
- Schwann cell

Saccule
- Hair cells
- Supporting cells
- Connective tissue

Utricle
- Hair cell
- Supporting cells
- Connective tissues

Anterior Crista
- Hair cell
- Supporting cells
- Epithelial cells
- Connective tissue

Horizontal Crista
- H ir cells
- Supporti g cells
- Epithelial cells
- Connective tissu

Posterior Crista
- Hair cells
- Supporting cells
- Epithelial cells
- Connecti e tissue

Scarpa s ganglion
- Ganglion cells
- Schwann cells

servation point in the reconstruction was determined for each of the following cell types inner hair cells, outer hair cells, inner supporting cells, Deiter s cells, inner pillar cells, outer pillar cells, Claudius cells, Hensen s cells, spiral ganglion cells, internal sulcus cells and external sulcus cells. Only the number of labeled cells was counted for Schwann cells, cells of Reissner s membrane epithelial cells of the basilar membrane [1] cells of the stria vascularis, cells of the spiral ligament, epithelial cells of the limbus and cells of the limbus stroma.

Analysis of the reconstruction was made with the aid of a computer program. The number of observations of a given cell type within a cochlea was considered to be proportional to the length within the cochlea of the tissue containing that cell type Those cell types which were further from the modiolus subtended the greatest arcs and were distributed over a greater length than those which were distributed closer to the modiolus (e g the number of bservatic ns fc r the spiral ligament was much greater than that of the spiral ganglion cells The data f r the cochlear reconstructions were transferred t unch cards and the information was processed so as to

[1] The [illegible] f [illegible] hold [illegible] ll which re fou d the scala tympa i pect f the basila me

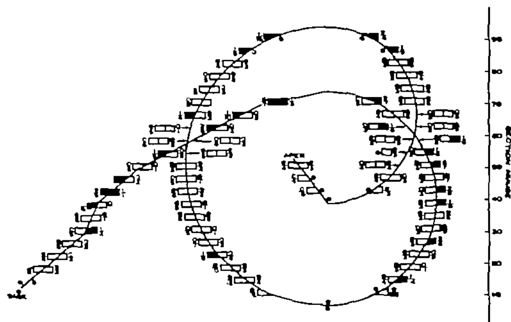


FIG. 4 Cochlea reconstruction of ear no 2644E 1 Outer hair cell are tabulated on the outside and inner hair cell on the inside f the spiral. The denominator is the number of cells present nd th umerator the umber of labeled cells present. Filled-in boxes indicated that labeled cells were present.

tabulate, for each cell type within the cochlea, the number of cells present, the number labeled, and the number of labeled cells divided by the number of cells present (percent labeling) In the classes of cells in which only the number of labeled cells were counted, a +1 was recorded at those observation points at which the cell was present The computer program was so designed as to eliminate observation points which had a zero in the cell present" category and compress the remaining observations. These remaining observations were then defined as the total "distance" that a particular cell type was found within the cochlear duct This length was given the arbitrary value of 1 0 The first observation nearest the basal turn was given the value of 0 and all distances between the base and apex were expressed as a fraction of 1 0 Thus the distance 0 to 0.2 would encompass the first 20% of those observations from the beginning of the basal turn in which there were no zeros recorded.

The distribution of the cells could be divided into 1 to 36 segments of equal length starting at the base and ending at the apex. Two examples of how the computer program worked are given below First, visualize a cochlea in which two cell types, A and B, are to be considered. This cochlea is to be divided into quarters. There were 100 observations for cell type A

TABLE 3 *Example of Computer Program*

Computer Input

Observation Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Number of Cells Present	0	0	2	2	2	3	0	0	3	2	2	2	0	2	0
	Base														Apex

Computer Output

I Compression of Observations and Elimination of Zeros

New Observation Number	1	2	3	4	5	6	7	8	9
Number of Cells present	2	2	2	3	3	2	2	2	2
	Base = 0.0				0.5				1.0 = Apex

II Number of observations at which cells were present = 9

III. Divide into two segments:

9/2 = 4.5 observations per segment

IV Calculation of number of cells present in each segment.

First segment (0.0 to 0.5)
Total of first 4.5 observations

Second segment (0.5 to 1.0)
Total of second 4.5 observations

New Observation Number	Number of cells Present	New Observation Number	Number of cells Present
1	2	5	1.5 = (3/2)
2	2	6	2
3	2	7	2
4	3	8	2
5	1.5 = (3/2)	9	2
	10.5 cells present from 0.0 to 0.5		9.5 cells present from 0.5 to 1.0

and 40 observations for cell type B. The first quarter (0.0 to 0.25) would include the first 25 observations for cell type A and the first 10 observations for cell type B. The second quarter (0.25 to 0.5) would contain the observations from the 26th to 50th observation point of cell type A and the 11th to 20th observations for cell type B, etc. The computer program was so arranged that if a segment ended so that it would contain a fraction of an observation, then the number of cells in the observation would be divided proportionately between the two segments. Table 3 illustrates an example of this feature of the computer program. This hypothetical cochlea has fifteen observation points. The cell type which was examined was found in nine of these observation points. The cochlea was divided into two equal segments, and the first segment contained one-half of the observations. These were the number of cells to be found at the first four and a half observation points. The observations of the first four points with half of

the observations at the fifth observation point were added to give a total of 10.5 cells in the basal half (0.0 to 0.5) of the cochlea. The remaining one half of the cells present at the fifth observation point were added to the number of cells found at the remaining four observation points to give a total of 9.5 cells in the apical half of the cochlea, i.e. from 0.5 to 1.0.

After each animal was analyzed, the data for all the animals for each day were combined and there was obtained for each cell type the total number of cells present in all ears, the mean number of labeled cells per ear and the total number of labeled cells in all ears divided by the total number of cells present in all ears (percent labeled). Each segment was analyzed in a similar fashion and a record was made of the total number of cells per segment, the mean number of cells per segment, the total number of labeled cells per segment, the mean number of labeled cells per segment divided by the total number of labeled cells in the cochleae (percent labeling activity per segment) and the number of labeled cells in a segment divided by the total number of cells in the segment (percent labeling per segment).

The posterior labyrinth was analyzed by counting the number of labeled cells for each cell type in every fourth section.

There were several indices used to measure the amount of labeling. The mean number of labeled cells for each cell type gave a measure of the amount of labeling which occurred. This parameter was useful for determining the time in development at which the greatest number of terminal mitoses of a given cell type occurred. There were large differences among the mean numbers of labeled cells of different types. These differences in the mean numbers of labeled cells could be attributed to the difference in the size of the cell populations, the DNA synthesis time (29), the cellular geometry (32), and other factors. In view of these differences other measures were used so that values for different cell types could be compared with one another. The first of these was called the "labeling activity" and was used to measure labeling on either a given day or in a segment. The total of all the means of the number of labeled cells for all the days or for all the cochleae within one day was the amount of labeling detectable by the methods used. The mean number of labeled cells which would occur per day or per segment was a fraction of this total. The fraction was called the labeling activity, was expressed as a percentage and was used in two ways. The first was % labeling activity per day

$$= \frac{\text{Mean number of labeled cells per day}}{\text{Total of mean number of labeled cells found on all days}} \times 100$$

The second was % labeling activity per segment

$$= \frac{\text{Number of labeled cells per segment per day}}{\text{Total number of labeled cells per day}} \times 100$$

Another measure was called "percent labeled" and was available only for those eleven cell types in which counts of both labeled and unlabeled cells were made $\% \text{ labeled} = \frac{\text{Number of labeled cells present per day}}{\text{Number of cells present per day}} \times 100$ The last index of labeling was a tabulation of the number of ears in which labeled cells of a given type were to be found At the beginning and the end of periods of terminal mitoses, not all ears would have labeled cells of the variety under study It was felt that results were more reliable when labeled cells were observed in all of the ears examined. This was especially important when there were low numbers of labeled cells observed

RESULTS

Cochlea

The cells of the cochlea may be classified into four groups according to the times during development at which terminal mitoses occurred. Many of the different classes of cells of the organ of Corti underwent most of their terminal mitoses on the 14th day of gestation. This was true for spiral ganglion cells, inner hair cells, outer hair cells, inner pillar cells, outer pillar cells, Deiter s cells, Hensen s cells, Claudius cells, inner supporting cells and external sulcus cells (Tables 4 5 and Figures 5 6, 7 8)

The second pattern of terminal mitoses was to be found in epithelial cells of the limbus and internal sulcus cells (Fig 9) These two cell types underwent the greatest amount of their terminal mitoses on the 16th day of gestation

The cells of the stria vascularis, spiral ligament and Schwann cells of the spiral ganglion had most of their terminal mitoses on the first day post partum (Fig. 10) All of these cell types still had cells undergoing terminal mitoses on the seventh day postpartum (Table 6)

The last group was characterized by a lack of a peak of terminal mitoses (Fig 11) This group consisted of cells of Reissner's membrane, epithelial cells of the basilar membrane and cells of the stroma of the limbus. The cells of Reissner s membrane underwent substantial amounts of terminal mitoses from the 13th day of gestation through the 3rd day postpartum The epithelial cells of the basilar membrane and cells of the stroma of the limbus had similar patterns of terminal mitosis.

The spiral ganglion cells had a greater cumulative percent of labeling activity in the ears exposed on the 12th and 13th day of gestation than any other cell type in the cochlea (Table 7) This indicates that a greater proportion of the spiral ganglion cells undergo terminal mitosis before other cells in the organ of Corti.

The stria vascularis, spiral ligament Schwann cells, cells of Reissner s membrane epithelial cells of the basilar membrane cells of the limbus stroma all had terminal mitoses occurring as late as the 7th day postpartum (Table 6) The remaining 11 cell types did not have any terminal mitoses in the late postpartum period.

Table 8 presents the number of labeled cells divided by the number of cells present for the 11 cell types for which counts of all cells were made. The total of these labeling percentages was an indication of the amount of labeling which occurred with the radioautographic techniques and exposure times used in these experiments. There is a fourfold difference in the

TABLE 4 *Number of Ears with Labeled Cells Present—Cochlea*

	Day of Exposure to Tritiated Thymidine										
	Gestation							Postpartum Day			
Cell Type	10	12	13	14	15	16	18	1	3	5	7
Inner hair c lls	0/1	3/5	4/8	8/8	4/6	2/6	1/6	0/3	0/2	0/2	0/3
Outer hair cells	0/4	3/5	8/8	8/8	0/6	5/6	0/6	0/3	0/2	0/2	0/3
Inner supporting cells	0/1	3/5	4/8	8/8	0/6	6/6	4/6	0/3	1/2	0/2	0/3
Deiter's cells	0/1	3/5	7/8	8/8	6/6	5/6	0/6	0/3	0/2	0/2	0/3
Inner Pillar cells	0/1	2/5	5/8	8/8	5/6	3/6	0/6	0/3	0/2	0/2	0/3
Outer Pillar cells	0/4	3/5	6/8	8/8	5/6	3/6	0/6	0/3	0/2	0/2	0/3
Claudius cells	0/1	4/5	6/8	8/8	0/6	6/6	1/6	0/3	0/2	0/2	0/3
Hensen s cells	0/4	3/5	7/8	8/8	0/6	5/6	0/6	0/3	0/2	0/2	0/3
Spiral ganglion cells	0/1	2/5	6/8	8/8	6/6	2/6	0/6	0/3	0/2	0/2	0/3
Internal Sulcus cells	0/1	1/5	4/8	8/8	0/6	0/6	4/6	0/3	0/2	0/2	0/3
External Sulcus cells	0/1	4/5	7/8	8/8	0/6	0/6	1/6	1/3	0/2	0/2	0/3
Reissner's membrane	0/1	2/5	0/8	8/8	0/6	0/6	0/6	3/3	2/2	2/2	3/3
Epithelium of Basilar membrane	0/4	1/5	4/8	8/8	6/6	0/6	6/6	3/3	2/2	0/2	1/3
Stria Vascularis	0/1	2/	5/8	8/8	0/6	0/6	6/6	3/3	2/2	2/2	3/3
Spiral Ligament	0/1	0/5	4/8	8/8	0/6	0/6	6/6	3/3	2/2	2/2	3/3
Limbus Epitheli m	0/1	1/7	2/8	8/8	6/6	6/6	6/6	0/3	1/2	0/2	0/3
Limbus Stroma	0/1	0/5	1/8	8/8	0/6	6/6	6/6	3/3	2/2	2/2	3/3
Schwann cells	0/1	2/5	4/8	8/8	0/6	0/6	0/6	3/3	2/2	2/2	3/3

Numerator = Number of ears with labeled cells.
Denominator = Number of ears observed.

cumulative percentage of labeling with spiral ganglion cells having the least and external sulcus cells having the greatest cumulative percentage of labeling

The cochlear duct was divided into five equal segments from the base (0.0) to the apex (1.0). The labeling activity per segment for all 18 cell types is found in Table 9 and graphic representations of the outer hair cells, inner pillar cells and spiral ganglion cells are illustrated in Figures 12, 13 and 14. The spatial distribution of labeling activity as a function of day of exposure to tritiated thymidine was examined. Two factors were considered in evaluating the results. *First, if there were always a greater* number f a given cell type in one segment then the percentage of labeling activity f r that segment could be high. This was controlled in the 11 cell type in which total counts were done by comparing the percent labeled per segment with the labeling activity per segment (Table 9). There were no marked discrepancies between these two measures of the spatial distribution of cell types within the adult cochlea. The interpretation of the

TABLE 5 Mean Number of *Labeled Cells per Day—Cochlea*

Cell Type	Day of Exposure to Tritiated Thymidine — Gestation 10	12	13	14	15	16	18	Postpartum 1	3	5	7	Total of Means
Inner hair cells	0	1.2	2.5	12.1	1	0.3	0.2	0	0	0	0	18.0
Outer hair cells	0	6.8	40.4	113.3	23.2	2.8	0	0	0	0	0	186.5
Inner supporting cells	0	2.0	8.0	46.4	12.3	17.8	10.3	0	0.5	0	0	97.3
Deiter's cells	0	4.0	11.6	73.0	9.5	4.0	0	0	0	0	0	105.1
Inner Pillar cells	0	0.8	8.6	39.8	2.	0.5	0	0	0	0	0	52.4
Outer Pillar cells	0	1.0	6.9	31.8	2.5	0.5	0	0	0	0	0	42.8
Claudius cells	0	10.6	18.6	80.3	35.8	16.0	0.5	0	0	0	0	161.8
Hensen's cells	0	4.0	1 .3	47.4	12.2	6.0	0	0	0	0	0	86.9
Spiral ganglion cells	0	17.8	83.4	120.6	22.0	0.7	0	0	0	0	0	244.5
Internal Sulcus cells	0	0.2	0.9	15.9	22.3	47.2	12.8	0	0	0	0	99.3
External Sulcus cells	0	4.2	19.9	45.4	29.7	23.8	0.2	0.1	0	0	0	123.3
Reissner's membrane	0	4.0	54.3	95.6	58.5	84.8	67.0	132.3	173.5	28.5	41.7	734.2
Epithelium of Basilar membran	0	1.6	2.5	38.9	62.7	90.7	71.3	89.0	27.0	0	0.7	384.4
Stria vascularis	0	2.6	9.0	93.1	95.5	89.0	39.5	770.0	438.5	93.0	45.0	1680.2
Spiral Ligament	0	0	7.1	104.9	216.5	279.3	577.0	2583.7	945.5	146.0	172.7	5002.7
Limbus Epithelium	0	0.2	1.1	47.4	92.8	157.3	22.7	0	2.5	0	0	324.0
Limbus Stroma	0	0	0.3	18.3	72.7	126.0	137.7	104.0	53.0	8.0	8.3	522.3
Schwann cells	0	0.6	2.3	20.4	38.0	55.3	77.8	1472.3	946.0	172.0	138.3	2961.0

data for the remaining seven cell types must be based solely upon shifts in the labelling activity per segment

The second factor was the mean number of labeled cells observed in all of the cochleae within an exposure day. When the mean number of labeled cells was small, then each cell had a large percentage of segmental labeling activity associated with it. Therefore, segmental distributions of labeling activity based on a small mean number of labeled cells should be interpreted with caution.

Three general patterns of terminal mitoses were noted with respect to position in the cochlea. The first group (*Group I, Table 9*) consisted of the cell types in which cells located in the apical segment of the adult cochlea underwent terminal mitoses first, and those located in the basal segment of the adult cochlea underwent terminal mitoses last. This group consisted of inner hair cells, outer hair cells, inner pillar cells, outer pillar cells,

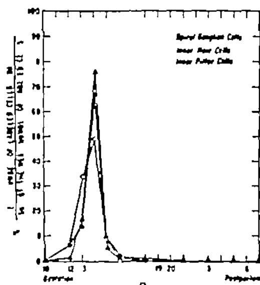


FIG. 5

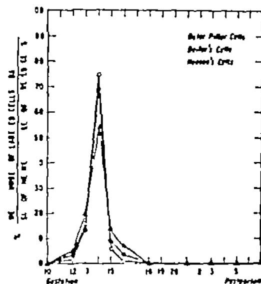
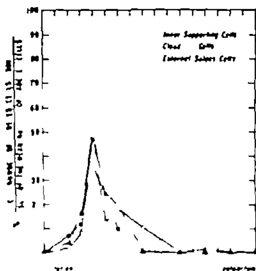


FIG. 6.

FIG. 5 Labelling acti it f piral g ngli n, in er hair d inn r pill r cells. Day = D f injecti f tritiated thymidin

FIG. 6 Labelling acti ity of ter pilla Deiter d Hensen cells. Day = D y f i jec- ti f triti ted thymidine



F

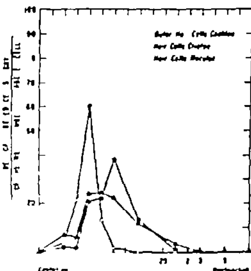


FIG. 8

FIG. 7 Label g cti it f i er upporti g Cl di nd tern l len ell D s = D y f i j f iti ted th midine

FIG. 8 Co f l beli g acti it f ter hai ll of chl a, h l cell f cri t nd hai m l D D y f i jection f t iti ted th midine

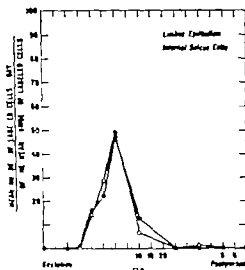


Fig. 9

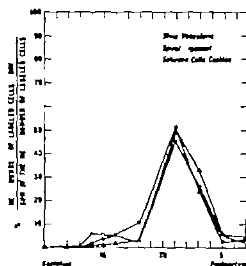


Fig. 10

Fig. 9 Labeling ctivity f limbu epithelium nd I ternal leu cells. Days = Day of I jecti n f tritiated thymidine

Fig. 10 Labeling acti ity f stria vascularis, piral ligament d the Schwann cells f the cochl a. Days = Day f I jection f triti ted thymidine

TABLE 6 *Cell Type Labeled on Postpartum Day 7*

Type	Mean Number of Labeled Cells Postpartum Day 7	% Labeling Activity Postpartum Day 7
Cochlea		
Reissner' membrane	41 7	5 7
Schwamm cells		
Spiral ganglion	138.3	4 7
Spiral ligament	172.7	3.4
Stria vascularis	45.0	2.7
Limbus stroma	8.3	1 6
Epithelium		
Basilar membrane	0.7	0.2
Posterior labyrinth		
Schwann cells		
Scarpa ganglion	92.0	10.2
Epithelial cells		
Crista	3.0	1.6
Connective tissue cells		
Cristae	8 6	2.2
Connective tissue cells		
Maculae	13 1	2.0
Supporting cells		
Maculae	0.3	0.1

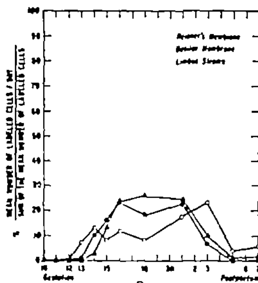


FIG. 11 Labeling acti ity of the cell f R i ner' membran the epithelial cell f the ba ila m mbrane and the cells f the limbu strom D ys—Day f i jectio f tritiated thymidine

Hensen s cells, Deiter s cells, and external sulcus cells (Figs. 12, 13) Three of the cell types followed a similar pattern of distribution except that there was a possible secondary shift to the apex among the youngest cells, i e., those cells which were labeled last The Claudius cells, inner supporting cells and internal sulcus cells make up this subgroup

The second group (Group II Table 9) consisted of the spiral ganglion cells, the Schwann cells, and the epithelial cells of the basilar membrane (Fig 14) The earliest labeled cells of this group i e., the oldest cells, were located in the basal segments. The terminal mitoses which occurred later in gestation or early neonatal life i.e., the younger cells, were located in the apical segments

The last group (Group III Table 9) consists of cells of the spiral liga ment stria vascularis, epithelium of the limbus, limbus stroma and Reiss ner s membrane These five cell types did not have any apparent systematic distribution of labeled cells related to the time of exposure to the tritiated thymidine These were five of the seven cell types in which total cell numbers were not counted and the determination of the percent labeled per segment w uld be needed before a definitive statement could be made

Posterior Labyrinth

The hair cells, upp rting cells epithelial cells and connective tissue cells of the three cristae were examined The cristae will be discussed together a the time and mean number f labeled cells in each class of cell was imil r Tabl 10 and Figs 15 16 17 18) The labeling activity of the hair and pporting cells f the cri tae fell wel a similar pattern

TABLE 7 *Cumulative Percent of Labeling Activity—Cochlea*

	Day of Exposure to Tritiated Thymidine										
	Gestation							Postpartum			
Cell Type	10	12	13	14	15	16	18	1	3	5	7
Inner hair cells	0	6.7	20.6	87.8	87.2	98.9	100	100	100	100	100
Outer hair cells	0	3.6	25.0	85.1	98.5	100	100	100	100	100	100
Inner supporting cells	0	2.1	10.3	58.0	70.6	88.9	99.5	99.5	100	100	100
Deiters' cells	0	2.8	17.7	87.0	98.0	100	100	100	100	100	100
Inner pillar cells	0	1.5	17.9	93.9	98.1	100	100	100	100	100	100
Outer pillar cells	0	2.3	18.4	92.9	98.7	100	100	100	100	100	100
Claudius' cells	0	6.6	18.1	67.7	89.8	99.7	100	100	100	100	100
Hensen cell	0	4.6	24.5	79.0	93.0	100	100	100	100	100	100
Spiral ganglion cells	0	7.2	41.3	90.6	99.6	100	100	100	100	100	100
Internal sulcus cells	0	0.2	1.1	17.1	39.6	87.1	100	100	100	100	100
External sulcus cells	0	3.4	10.5	66.3	80.4	99.7	99.9	100	100	100	100
Reissner' membrane	0	0.5	7.9	20.9	28.9	41.0	48.8	66.8	90.4	94.3	100
Epithelium of basilar membrane	0	0.4	1.1	11.2	27.5	51.1	69.6	92.8	90.8	99.8	100
Stria vascularis	0	0.2	0.7	6.5	12.2	17.5	19.9	63.7	91.6	97.2	100
Spiral ligament	0	0	0.1	2.2	6.5	12.0	23.5	74.8	93.6	96.5	100
Limbus epithelium	0	0.1	0.4	15.0	43.6	92.1	99.1	99.1	100	100	100
Limbus stroma	0	0	0.1	3.0	16.9	41.0	67.4	87.2	97.4	98.4	100
Schwann cells	0	>0.1	0.1	0.8	2.0	3.9	6.5	56.2	69.5	93.3	100

(Fig 19) There was very little labeling in the ears exposed on the 12th and 13th days of gestation. The labeling activity increased on the 14th day of gestation, reached a maximum on the 16th day of gestation, and continued into the postpartum period. The maximum on the 16th day of

TABLE 8 *Total Percent Labeled*

Cell Type	Total Percent Labeled for all Exposure Days
External sulcus cells	42.6
Outer hair cells	38.1
Inner pillar cells	33.7
Internal sulcus cells	32.4
Claudius' cells	27.8
Inner supporting cells	26.6
Hensen cells	26.6
Outer pillar cells	26.4
Deiters' cells	24.4
Inner hair cells	12.6
Spiral ganglion cells	11.8

TABLE 9 *Segmental Labeling*

	Segment	Day of Exposure to Tritiated Thymidine — Gestation: 10	12	13	14	15	16	18	Postpartum: 1	3	5	7
GROUP I						*Inner Hair Cells*						
% Labeled	0.2	0	0	0	5.0	7.9	0	0	0	0	0	0
per segment	0.4	0	0.6	0.4	11.0	0.5	0	0	0	0	0	0
	0.6	0	0.5	1.0	16.5	0	0.9	0.5	0	0	0	0
	0.8	0	0.6	3.4	5.6	0	0	0	0	0	0	0
	1.0	0	1.4	3.5	0	0	0	0	0	0	0	0
% Labeling	0.2	0	0	0	9.3	90.0	0	0	0	0	0	0
Activity	0.4	0	16.7	5.0	29.5	10.0	0	0	0	0	0	0
per segment	0.6	0	16.7	15.0	41.0	0	100	100	0	0	0	0
	0.8	0	16.7	35.0	12.0	0	0	0	0	0	0	0
	1.0	0	50.0	45.0	8.2	0	0	0	0	0	0	0
						Outer Hair Cells						
% Labeled	0.2	0	0	1.2	19.0	14.5	3.6	0	0	0	0	0
per segment	0.4	0	0	3.5	38.1	9.0	0	0	0	0	0	0
	0.6	0	0.7	5.2	26.6	3.0	0	0	0	0	0	0
	0.8	0	1.1	10.4	19.1	2.9	0	0	0	0	0	0
	1.0	0	5.1	17.1	10.8	0.4	0	0	0	0	0	0
% Labeling	0.2	0	0	2.4	12.9	34.3	100	0	0	0	0	0
Activity	0.4	0	0	9.7	31.7	40.8	0	0	0	0	0	0
per segment	0.6	0	14.7	17.9	30.7	13.0	0	0	0	0	0	0
	0.8	0	15.3	24.7	15.2	10.3		0	0	0	0	0
	1.0	0	70.0	45.3	9.5	1.6	0	0	0	0	0	0
						Inner Pillar Cells						
% Labeled	0.2	0	0	0.7	16.4	9.2	1.5	0	0	0	0	0
per segment	0.4	0	0	2.5	35.9	0.5	0	0	0	0	0	0
	0.6	0	0	3.9	29.1	0	0	0	0	0	0	0
	0.8	0	0.5	5.8	20.3	0.6	0	0	0	0	0	0
	1.0	0	1.7	10.2	9.2	0	0	0	0	0	0	0
% Labeling	0.2	0	0	2.6	12.5	87.5	100	0	0	0	0	0
Activity	0.4	0	0	11.9	36.0	6.3	0	0	0	0	0	0
per segment	0.6	0	0	20.3	28.9	0	0	0	0	0	0	0
	0.8	0	25.0	22.3	15.1	6.3	0	0	0	0	0	0
	1.0	0	75.0	42.9	7.5	0	0	0	0	0	0	0
						Outer Pillar Cells						
% Labeled	0.2	0	0	0.5	14.2	9.5	1.7	0	0	0	0	0
per segment	0.4	0	0	1.8	30.8	0.4	0	0	0	0	0	0
	0.6	0	0	5.5	28.3	1.3	0	0	0	0	0	0
	[illegible]	0	0.6	6.0	13.1	0	0	0	0	0	0	0
	[illegible]	[illegible]	2.1	6.8	8.3	0	0	0	0	0	0	0
% Labeling	[illegible]	[illegible]		1.8	13.3	81.3	100	0	0	0	0	0
Activity	[illegible]			9.8	32.2	5.3	0	0	0	0	0	0
per segment	[illegible]	0		29.5	33.3	13.3	0	0	0	0	0	0

TABLE 9 Cont

	Seg-ment	Day of Exposure to Tritiated Thymidine — Gestation 10	12	13	14	15	16	18	Postpartum 1	3		7
	0.8	0	20.0	23.5	12.8	0	0	0	0	0	0	0
	1.0	0	80.0	33.5	8.5	0	0	0	0	0	0	0
					Hensen Cells							
% Labeled	0.2	0	0	0.5	16.1	7.6	3.7	0	0	0	0	0
per segment	0.4	0	0	2.7	21.7	8.4	2.1	0	0	0	0	0
	0.6	0	0.6	4.2	19.0	3.3	0.5	0	0	0	0	0
	0.8	0	0	5.1	11.5	0.3	1.3	0	0	0	0	0
	1.0	0	5.0	11.6	4.5	0	0.9	0	0	0	0	0
% Labeling	0.2	0	0	1.4	18.3	30.1	38.9	0	0	0	0	0
Activity	0.4	0	0	10.9	31.5	49.3	27.8	0	0	0	0	0
per segment	0.6	0	10.0	16.7	28.0	19.2	5.6	0	0	0	0	0
	0.8	0	0	20.4	15.9	1.4	16.7	0	0	0	0	0
	1.0	0	90.0	50.6	6.2	0	11.1	0	0	0	0	0
					Deiters' Cells							
% Labeled	0.2	0	0	0.4	14.6	10.0	5.3	0	0	0	0	0
per segment	0.4	0	0	1.6	23.4	3.1	0	0	0	0	0	0
	0.6	0	0.3	1.2	19.1	1.1	0	0	0	0	0	0
	0.8	0	0	5.8	13.5	0.6	0	0	0	0	0	0
	1.0	0	5.0	8.5	9.9	0	0	0	0	0	0	0
% Labeling	0.2	0	0	1.7	13.9	56.5	100	0	0	0	0	0
Activity	0.4	0	0	10.4	32.1	30.2	0	0	0	0	0	0
per segment	0.6	0	5.0	9.2	27.3	9.5	0	0	0	0	0	0
	0.8	0	0	28.9	15.1	3.9	0	0	0	0	0	0
	1.0	0	93.0	49.7	11.6	0	0	0	0	0	0	0
					External Sulcus Cells							
Labeled	0.2	0	2.9	0.2	9.1	10.6	15.9	0	0	0	0	0
per segment	0.4	0	0	1.3	15.4	9.4	4.5	0	0.5	0	0	0
	0.6	0	0.3	2.2	22.8	13.4	6.4	0	0	0	0	0
	0.8	0	0	12.4	31.8	11.3	10.0	0.5	0	0	0	0
	1.0	0	5.5	14.2	14.0	7.5	5.6	0	0	0	0	0
Labeling	0.2	0	38.1	0.6	12.8	19.0	40.4	0	0	0	0	0
Activity	0.4	0	0	5.2	18.7	20.3	12.0	0	100	0	0	0
per segment	0.6	0	4.8	6.8	26.8	21.5	18.9	0	0	0	0	0
	0.8	0	0	38.9	21.5	22.2	17.1	100	0	0	0	0
	1.0	0	57.1	48.6	20.1	13.9	13.6	0	0	0	0	0
					Claudius' Cells							
% Labeled	0.2	0	<0.1	0.3	9.2	10.7	4.2	0	0	0	0	0
per segment	0.4	0	0.2	0.7	13.1	7.3	2.0	0	0	0	0	0
	0.6	0	0.2	2.0	16.3	4.9	1.8	0	0	0	0	0
	0.8	0	0.7	4.8	15.7	6.0	2.7	0.2	0	0	0	0
	1.0	0	6.8	7.9	12.9	4.3	2.0	0.2	0	0	0	0

TABLE 9 *Cont*

		Day of Exposure to Tritiated Thymidine										
		Gestation							*Postpartum*			
	Seg-m nt	10	12	13	14	15	16	18	1	3	5	7
% Labeling	0 2	0	0 4	1.3	10 8	24.3	28.3	0	0	0	0	0
A tivity	0 4	0	3.4	5.4	20.2	29 2	18.5	0	0	0	0	0
per segment	0 6	0	1 9	14.0	28.2	16.1	14 6	0	0	0	0	0
	0 8	0	9 1	31 0	22.4	18.7	23 1	66 7	0	0	0	0
	1 0	0	85.3	48.3	18.3	11 7	15 4	33.3	0	0	0	0
					Inne Support ng Cells							
% Labeled	0 2	0	0.3	0 2	12.7	10 4	5.5	0 9	0	0	0	0
per segme t	0 4	0	0	1 4	20.8	5.8	7 0	0.2	0	0 6	0	0
	0 6	0	0	2.2	18 6	1 7	6 3	1 4	0	0	0	0
	0.8	0	0	2.8	7.8	0.5	0.8	4.3	0	0	0	0
	1 0	0	1 9	3.2	7 0	1 1	1.3	5 7	0	0	0	0
% Labeling	0.2	0	10 0	1 6	15 0	41 1	19 8	4.8	0	0	0	0
Activity	0 4	0	0	14 1	32.8	38.6	37 0	1 6	0	100	0	0
per segment	0 6	0	0	24 7	29.8	10.8	33.1	11 3	0	0	0	0
	0 8	0	0	25 3	11 7	2.7	3 7	31 9	0	0	0	0
	1 0	0	90.0	34 4	10 7	6.8	6.5	50.3	0	0	0	0
					Internal Sulcus Cells							
% Labeled	0.2	0	0	0	9 0	8 9	16.3	0	0	0	0	0
per segment	0 4	0	0	0.3	6.5	12.0	24 6	0.3	0	0	0	0
	0.6	0	0	0 4	7 1	11 6	17 0	2.1	0	0	0	0
	0.8	0	0	0.2	3 1	4.8	7 1	0	0	0	0	
	0.8	0	0	0 2	3 1	4.8	6 4	7 1	0	0	0	0
	1 0	0	0.3	0 4	0.4	3 2	4 6	11 6	0	0	0	0
% Labeling	0.2	0	0	0	25 0	14.2	16.3	0	0	0	0	0
Activity	0 4	0	0	28 6	32.0	30 0	39.3	1 3	0	0	0	0
per segment	0 6	0	0	28.6	29.3	34 6	27 7	9 4	0	0	0	0
	0.8	0	0	14.3	12.0	12.2	9 6	29 9	0	0	0	0
	1 0	0	100 0	28 6	11 7	9 0	7 1	50.5	0	0	0	0
GROUP II					*Spiral Ganglion Cells*							
% Labeled	0.2	0	2.0	2.0	0	>0 1	0	0	0	0	0	0
per segment	0 4	0	1 0	7 6	0 2	0 1	0	0	0	0	0	0
	0 6	0	1.2	5 7	2.4	0 4	0 1	0	0	0	0	0
	0 8	0	0.3	1.3	15.2	0.5	0	0	0	0	0	0
	1 0	0	<0 1	0 2	16 6	4 1	0 1	0	0	0	0	0
% Labeling	0.2	0	44 9	10 6	0	0.8	0	0	0	0	0	0
Activity	0 4	0	22.5	65.0	0 6	3.0	0	0	0	0	0	0
per segment	0 6	0	25.6	27.5	7 6	8 6	50 0	0	0	0	0	0
	0 8	0	8 7	5.9	50 1	9.5	0	0	0	0	0	0
	1 0	0	0 2	1 0	41 7	78 0	50 0	0	0	0	0	0
					Schwann Cells							
~ Labeling	0.2	0	60.7	44 4	53 7	29 1	34 3	24.2	24 6	21 0	9 0	15.1
Activity	0 4	0	0	6 6	20 5	30 7	30 1	28.5	22.9	24 0	14.9	25.1

TABLE 9 *Cont*

		Day of Exposure to Tritiated Thymidine										
		Gestation							Postpartum			
	Segment	10	12	13	14	15	16	18	1	3	5	7
per segment	0.6	0	0	38.9	5.8	15.9	22.7	21.6	22.6	19.3	10.2	15.5
	0.8	0	33.3	5.6	13.6	17.0	8.2	12.8	17.1	19.7	21.3	23.2
	1.0	0	0	5.8	6.4	7.2	4.8	12.9	13.0	16.0	44.5	21.1
		Epithelium of Basilar Membrane										
Labeling	0.2	0	0	0	53.8	31.0	23.8	7.0	13.5	0	0	0
Activity	0.4	0	0	45.0	25.9	42.1	36.6	23.8	9.7	3.7	0	0
per segment	0.6	0	0	20.0	16.2	18.0	21.7	11.0	12.3	3.7	0	0
	0.8	0	0	35.0	2.6	5.3	10.4	32.0	21.3	24.1	50.0	0
	1.0	0	0	0	1.6	2.7	7.7	26.4	43.2	68.5	50.0	0
GROUP III		*Spiral ligament*										
* Labeling	0.2	0	0	5.3	20.7	25.6	27.6	31.0	28.4	29.8	25.0	22.8
Activity	0.4	0	0	8.8	20.9	33.0	32.4	28.8	23.7	28.3	28.3	33.6
per segment	0.6	0	0	7.0	21.6	20.8	23.4	19.2	19.0	14.5	19.5	22.2
	0.8	0	0	22.5	14.4	13.2	11.5	15.0	15.5	15.6	14.5	17.8
	1.0	0	0	56.5	22.5	7.4	5.2	6.1	11.3	11.8	12.8	3.7
		Stria vascularis										
* Labeling	0.2	0	7.7	41.7	26.7	16.3	7.9	21.8	19.2	20.2	12.0	11.9
Activity	0.4	0	0	20.6	33.6	31.5	17.9	25.0	21.2	24.1	14.3	34.1
per segment	0.6	0	0	4.4	16.8	25.1	48.5	16.8	27.0	20.5	22.2	23.7
	0.8	0	0	18.1	11.6	12.1	19.0	11.6	16.8	18.4	28.9	15.6
	1.0	0	92.3	15.3	11.3	15.1	8.8	25.0	15.9	16.9	22.6	14.8
		Limbus Epithelium										
Labeling	0.2	0	0	11.1	27.4	18.7	19.3	0.7	0	0	0	0
Activity	0.4	0	0	11.1	32.4	25.8	23.3	1.5	0	0	0	0
per segment	0.6	0	0	11.1	21.1	32.3	38.6	4.4	0	0	0	0
	0.8	0	0	0	9.9	11.3	10.0	17.5	0	100	0	0
	1.0	0	100	66.7	9.2	12.0	8.8	73.9	0	0	0	0
		Limbus Stroma										
Labeling	0.2	0	0	60.0	41.0	28.3	23.7	21.4	16.3	27.4	20.0	12.0
Activity	0.4	0	0	40.0	29.7	25.8	37.4	24.2	17.2	19.8	40.0	4.0
per segment	0.6	0	0	0	16.2	35.1	24.6	27.5	18.1	17.7	20.0	36.0
	0.8	0	0	0	8.2	7.8	7.1	13.4	17.7	16.2	0	8.0
	1.0	0	0	0	4.9	3.0	5.2	13.5	30.6	18.9	20.0	40.0
		Reissner' Membrane										
Labeling	0.2	0	40.0	15.1	36.9	29.0	30.8	13.0	23.3	24.4	15.8	23.4
Activity	0.4	0	0	32.2	23.4	15.3	26.3	10.6	20.4	23.8	19.3	28.8
per segment	0.6	0	20.0	43.5	26.5	36.6	36.4	16.1	23.6	23.5	41.1	20.3
	0.8	0	0	5.3	8.4	14.8	8.1	18.4	9.3	13.1	15.4	10.0
	1.0	0	0	3.9	5.7	4.3	8.6	41.8	21.5	15.3	8.4	17.6

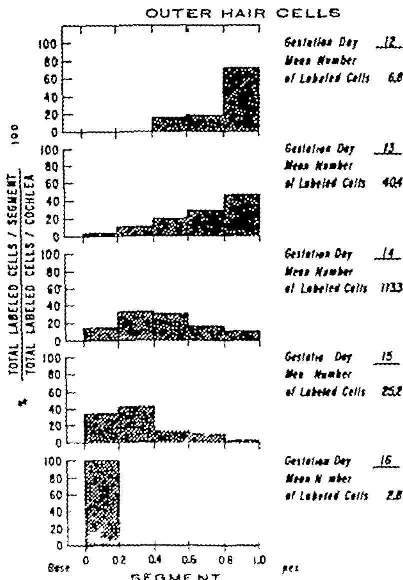


FIG. 12. P ition f label d outer hai cell withi the mature cochlea. Gestati n d y i the day f injection f the tritiated thymidine

gestation was 38 4 % labeling activity for the hair cells and 35 4 % labeling activity for the supporting cells. Both of these maxima were smaller than those noted for similar cell types in the cochlea.

The connective tissue cells and the epithelial cells of the cristae had low percentages of labeling activity on the 14th and 15th days of gestation (Fig 19) The maximal percentage of labeling activity was found in the ears exposed on the first and third days postpartum. Both of these cell types had terminal mitoses as late as the 7th day postpartum (Table 6) Their pattern of terminal mitosis was similar to that of the stria vascularis, spiral ligament and Schwann cells

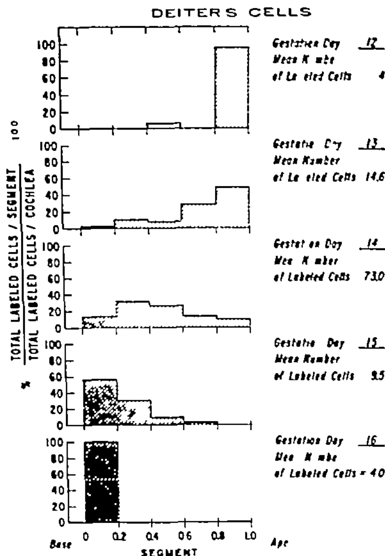


FIG. 13. Position of l beled Deiter cells withi the mature cochlea Gest ti day is the d y f injectio f the tritiated thymidine

The mean number of terminal mitoses of the two maculae were similar with one exception (Table 10 and Figs. 20 21) The mean number of labeled connective tissue cells (Fig. 22) in the macula of the saccule was much greater than the mean number found in the macula of the utricle.

Figure 23 illustrates the combined percent labeling activity of the cell types in the two maculae. The hair cells and supporting cells follow a similar pattern of terminal mitosis. The percent of labeling activity was between 5 and 10% in the ears exposed on the 12th and 13th day of gesta tion There was an increase in labeling activity for both cell types in the ears exposed on the 14th, 15th and 16th days of gestation. The percent of

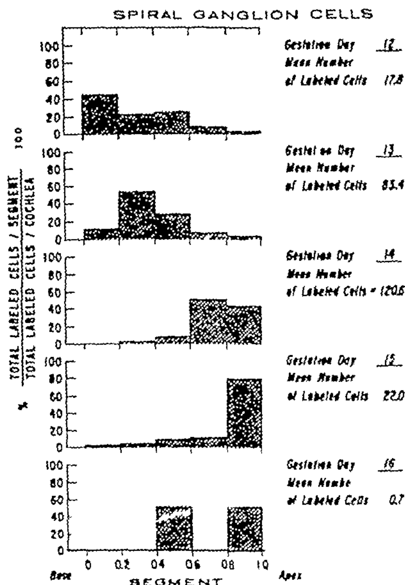


Fig. 14 Position f labeled piral ganglion cell withi the mature cochlea Gest ti n day is the day of injecti n f the tritiated thymidin

labeling activity never exceeded 25% per day of exposure for either the hair or supporting cells of the maculae. The labeling activity persisted until the fifth day postpartum for the hair cells and until the seventh day post partum for the supporting cells.

The pattern of labeling activity (Table 10 and Fig 23) for the connective tissue cells of the two maculae was similar to that of the cristae in that the maximum percent of labeling activity was noted on the first and third days postpartum The terminal mitoses of the connective tissue cells of the two maculae continued until the seventh day postpartum

The labeling activity of the ganglion cells and Schwann cells of Scarpa s

TABLE 10 Number of Ears with Labeled Cells Present—*Posterior Labyrinth*

	Day of Exposure to Tritiated Thymidine										
	Gestation							Postpartum			
Cell Type	10	12	13	14	15	16	18	1	3	5	7
Horizontal crista											
Hair cells	0/4	2/5	3/8	8/8	6/6	6/6	6/6	0/3	0/2	0/2	0/3
Supporting cells	0/4	2/5	1/8	8/8	6/6	6/6	6/6	0/3	0/2	0/2	0/3
Connective tissue	0/4	1/5	0/8	/8	6/6	6/6	6/6	3/3	2/2	2/2	3/3
Epithelial cells	0/4	0/5	1/8	3/8	3/6	4/6	6/6	3/3	2/2	2/2	1/3
Anterior crista											
Hair cells	0/4	2/5	4/8	8/8	6/6	6/6	6/6	2/3	0/2	0/2	0/3
Supporting cells	0/4	2/5	5/8	8/8	6/6	6/6	6/6	2/3	0/2	0/2	0/3
Connective tissue	0/4	0/5	4/8	6/8	6/6	6/6	6/6	3/3	2/2	2/2	2/3
Epithelial cells	0/4	0/5	0/8	5/8	6/6	6/6	4/6	3/3	2/2	1/2	2/3
Posterior crista											
Hair cells	0/4	2/5	1/8	8/8	6/6	6/6	6/6	1/3	0/2	0/2	0/3
Supporting cells	0/4	1/5	6/8	7/8	5/6	6/6	6/6	2/3	1/2	0/2	0/3
Connective tissue	0/4	1/5	0/8	7/8	6/6	6/6	6/6	3/3	2/2	1/2	3/3
Epithelial cells	0/4	0/5	1/8	3/8	2/6	6/6	4/6	3/3	2/2	1/2	1/3
Utricle macula											
Hair cells	0/4	2/5	6/8	8/8	6/6	6/6	6/6	3/3	0/2	0/2	0/3
Supporting cells	0/4	2/5	4/8	8/8	6/6	6/6	6/6	3/3	1/2	0/2	0/3
Connective tissue	0/4	0/5	0/8	6/8	6/6	6/6	6/6	3/3	2/2	1/2	3/3
Saccule macula											
Hair cells	0/4	3/5	6/8	8/8	6/6	6/6	6/6	3/3	2/2	1/2	0/3
Supporting cells	0/4	2/5	7/8	8/8	6/6	6/6	6/6	3/3	2/2	1/2	1/3
Connective tissue	0/4	0/5	1/8	7/8	6/6	6/6	6/6	3/3	2/2	1/2	3/3
Scarpa ganglion											
Ganglion cells	0/4	4/5	1/8	1/8	1/6	0/6	1/6	0/3	0/2	0/2	0/3
Schwann cells	0/4	2/5	5/8	8/8	6/6	6/6	6/6	3/3	2/2	2/2	3/3

Numerator = Number of ears with labeled cells.
Denominator Number of ears observed.

ganglion is illustrated in Figure 24 The Scarpa s ganglion cells underwent 90 % of their labeling activity on the 12th day of gestation Labeled ganglion cells occurred in 4 of the 5 ears exposed on the 12th day of gestation (Table 10) *During the 13th day of gestation 6.2%* of labeling activity occurred in one of eight ears. An occasional labeled Scarpa s ganglion cells was seen on the 14th, 15th and 18th day of gestation. The Schwann cells of Scarpa s ganglion had a low but gradually increasing, percentage of labeling activity until the day of birth when 33.8% of the labeling activity was found (Fig 24) On the third day postpartum 34.5% labeling activity was observed and 10.2% of the terminal mitoses of the Schwann cells were noted on the th day postpartum.

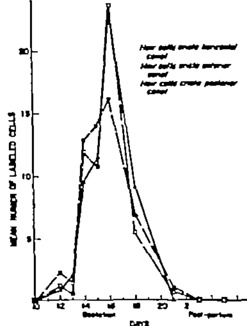


Fig. 15

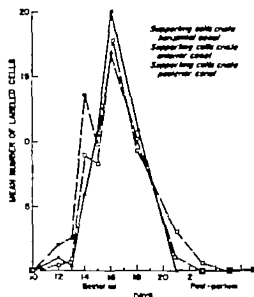


Fig. 16.

Fig. 15. Mean number of labeled hair cells in the three cristae. Days = D v of injection of tritiated thymidine

Fig. 16. Mean number f labeled s pporting cell in the three cristae. D vs = D v of injection of tritiated thymidin

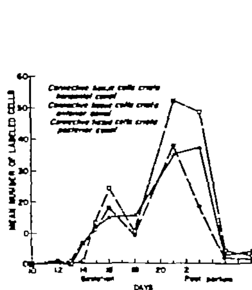


Fig. 17

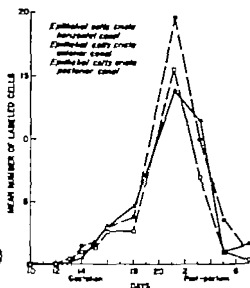


Fig. 18.

Fig. 17 Mean n mber f labeled co necti ti su cells in the three cristae D ys = Day f I jection of tritiated thymidine

Fig. 18. Mea number of labeled epithell l cells in th three crista D vs = Day f I jection of tritiated thymidin

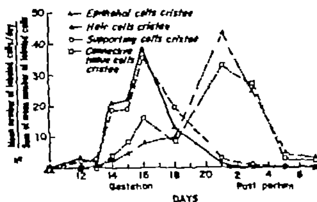


FIG. 19 Labelling acti ity f the hair upporting, connective tiss and epithelial cell of the three cristae Days = Day of i jection of tritiated thymidine

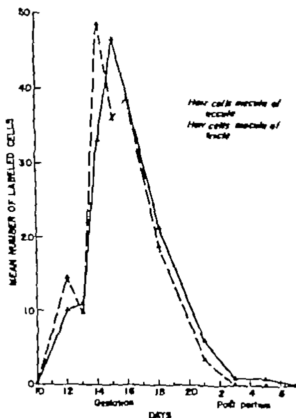


FIG. 20 Mean number of labeled hair cells of the two maculae D ys = Day of injection of tritiated thymidine

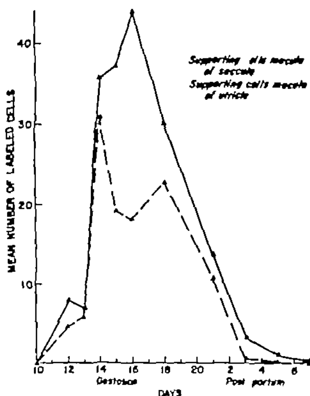


Fig. 21 Mean number of labeled upporting cell of the two maculae Days = D y f injection f triti ted thymidine

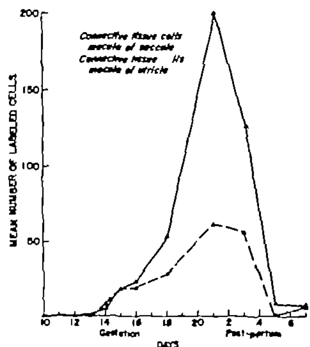


Fig. 22. Mean n mber f l beled connective ti u cells of the two macul D ys = D y of injection of t itiated th midi e

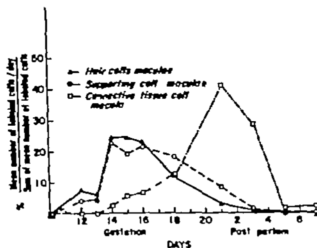


Fig. 23. Labeling activity f the hal supporting and connectiv tissu cells of the two maculae Days = D y of injection f tritiated thymidine

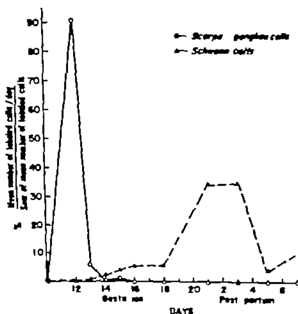


Fig. 24 Labelling activity of the Scarpa ganglion nd Schwann cell of Scarpa's ganglion. Days = Day of injection f tritiated thymidin

DISCUSSION

No terminal mitoses were detected in the ears exposed to tritiated thymidine on the 10th day of gestation Previous work (56) has shown that there is transplacental spread of tritiated thymidine as early as the ninth day of gestation. However the possibility that there was not any uptake of tritiated thymidine on the tenth day of gestation was investigated Two CBA-J mice in their tenth day of pregnancy were injected intraperitoneally with the standard dose of tritiated thymidine They were sacrificed one hour after injection and the embryos prepared for radioautography The resultant radioautographs of the ten-day old embryos showed heavy labeling in the otic vesicle It is probable that cells labeled on the tenth day of gestation underwent so many cellular divisions that there was no label detectable when the ears were examined 24 days later on the 14th day postpartum

The abscissae of the graphs in the preceding pages were in days. These time intervals were not constant in that each day was examined from gestation day 12 to gestation day 16 but there were either two or three day intervals between the data points for the other days. In some instances the number of labeled cells would have been much greater if days had not been omitted from the experimental design This would result in a lowering of the percent of labeling activity on a given day The large maxima of percent labeling activity found for the cells of the cochlea in the ears exposed to tritiated thymidine on the 14th day of gestation would not be greatly affected as there were very few labeled cells observed at times when every other or every third day was sampled. The greatest effect would be in those cells, e.g the hair cells of the maculae, cristae, etc., in which there were a large number of labeled cells observed at the time periods when every second or every third day was sampled The curve for these cells would be lower

Eleven cell types (Table 6) were noted to have terminal mitoses on the seventh day postpartum It was possible that some of these cell types continued to undergo mitoses during adult life If there were many of these cell types undergoing continual mitosis, then the percent of labeling activity would be lower because further cell divisions would dilute the label In acute studies with tritiated thymidine in adult animals Koburg (26) found evidence of a low level of mitotic activity in the cells of the spiral ligament, stria vascularis, epithelium of the basilar membrane epithelium of the limbus, stroma of the limbus, and Reissner s membrane These cells were all in the group of the eleven cell types which still showed terminal mitoses

on the seventh day postpartum (Table 6) The number of cells involved in these mitoses occurring in the mature cochlea was small and this should not substantially affect the pattern of terminal mitosis which was obtained in the present study

The time during which the labeled thymidine was available to the dividing cells was assumed to be one hour after injection (9 10 22, 29 30 34 46) The cells which remained labeled in the mature labyrinth were those which were in the DNA synthetic phase during the hour in which the tritiated thymidine was available Previous workers (22) have estimated that if a cell undergoes three or four additional divisions after exposure to tritiated thymidine, then the label will be so diluted as to be undetected by the conventional radioautographic techniques. It would appear that those cells which remained labeled in the mature labyrinth had undergone no more than 3 or 4 terminal mitoses. The heavily labeled cells had, at the most undergone one division after the uptake of tritiated thymidine Some of the labeled cells found in the labyrinth exposed on the 12th day of gestation (Fig 2 A) were lightly labeled and probably represent second third and fourth cellular divisions. The labeled cells seen in the ears exposed in the postpartum period were heavily labeled, and this was probably due to a greater concentration of tritiated thymidine available to the inner ear and to the cessation of cell division

A general observation was that the amount of label per cell was greater in those ears which were exposed to tritiated thymidine during the end of the period of terminal mitosis. For example, the apical hair cells of the cochlea on the 12th day of gestation had fewer grains per nucleus than those found in the basal turn of the cochlea labeled on the 16th day of gestation (Fig 2 A, 2 B) The time of cessation of cell division for a given cell type was determined more accurately than the time of the beginning of the period of terminal mitoses, because of the ability to detect the third and fourth cell divisions A difference in the number of grains per nucleus between different cell types was noted (Figs 1 2, 3) which may be accounted for by the physical difference in the cells (32) and by differences in the duration of the DNA synthetic phase (29)

There was a difference in the time of terminal mitoses for the hair and supporting cells of the cochlea and those of the posterior labyrinth (Fig 8) The hair and supporting cells of the cochlea underwent terminal mitoses before those of the posterior labyrinth The temporal pattern of terminal mitoses in the cochlea also differed (Figs. 5 6 7 8 9) There were sharp peaks of terminal mitoses in the cells of the organ of Corti in animals exposed to label on the 14th and 16th days of gestation. The hair and supporting cells of the posterior labyrinth underwent the bulk of their terminal mitoses over a five day period from the 14th to the 18th day of gestation and were characterized by comparatively modest maxima of labeling activity the hair and supporting cells of the maculae had smaller maxima than those of the cristae (Figs. 8, 19 23) This different time

pattern of terminal mitoses may make the organ of Corti more susceptible to an embryological insult at a given time than the vestibular apparatus. Several types of embryological insults occurring on the 14th day of gestation could interfere with cellular division This would damage almost the entire organ of Corti but have little effect on the vestibular apparatus. This difference in terminal mitoses of the two portions of the membranous labyrinth may have its clinical expression in the large numbers of congenitally deaf patients who have normal or near normal vestibular responses (44)

There were similarities in the pattern of terminal mitoses between the cochlea and the vestibular apparatus. The ganglion cells of Scarpa s ganglion underwent their terminal mitoses before the other portions of the vestibular apparatus (Figs. 19 23 24) The spiral ganglion cells showed a similar tendency to be the earliest group of cells to undergo terminal mitoses within the cochlea (Table 7) It would appear that the ganglion cells of the eighth nerve were the first cells to undergo terminal mitosis and consequently become the oldest cells of the inner ear The data indicate that the ganglion cells of Scarpa s ganglion undergo terminal mitosis before those of the spiral ganglion. This observation is in agreement with Streeter's (53) finding that in man the cells of the Scarpa s ganglion were identifiable somewhat earlier than those of the spiral ganglion

Most studies (5 8, 41 57 58) have shown that the cytological maturation of the organ of Corti begins at the basal end and proceeds to the apex Bélanger s (6) study is an exception to these other reports The position of the cells in the mature organ of Corti which underwent their terminal mitoses at different times, in part, presents a different pattern of development. The cells of the organ of Corti, that is, the hair cells, the pillar cells and Deiter s cells, were distributed in such a way that the oldest cells, the cells which undergo terminal mitoses first were at the apex and the youngest cells, the cells which undergo terminal mitoses last, were at the base The apical cells wait longer after they have undergone terminal mitoses before they reach their mature form than do the hair cells located in the basal turn (Figs. 12, 13)

The observation that the spiral ganglion cells underwent their terminal mitoses starting at the base and ending at the apex (Fig 14) suggests that the spiral ganglion cells could be responsible for inducing the morphological changes within the organ of Corti Tello (54) has noted in the mouse, by means of silver stains, that portions of the afferent fibers of the cochlea innervate the hair cells beginning at the basal turn It takes several days for the afferent innervation to reach the apex. The afferent innervation of the hair cells could play a role in initiating the differentiation of the cells of the organ of Corti

Rossi (43) has studied the pattern of innervation of the efferent fibers in the guinea pig with the acetylcholinesterase stains. The efferent fibers also innervate the base first and proceed to the apex. The electron microscopic observations of Kikuchi and Hilding (24) in the Shaker 1 mouse

demonstrate that identifiable efferent innervation does not occur in the shaker 1 until the 14th day postpartum, which is several days after the cochlea has achieved its cytological differentiation. It would appear from these observations that the efferents could not be primarily responsible for the cellular differentiation of the organ of Corti although they may be involved in the formation of the spaces of Nuel

Another point to be considered is what aspect of cytological differentiation is being studied. The work of Wada (67) and Weibal (68) was based on light microscopy They described the details of cellular development and the dimensions of the developing cochlear duct Kikuchi and Hilding (23) and Kimura (25) have shown with the electron microscope that cytological differentiation of the hair cells occurs early in the mouse They reported that the kinocilia of the hair cells were apparent at the first day postpartum. There is no information concerning the topographical appearance or disappearance of the kinocilia in the cochlea and this aspect of differentiation would be of great interest The histochemical correlates of cellular differentiation should also be considered in establishing the topographical pattern of differentiation. Some aspects of this have been described by Titova (55) and Milaire (37)

The observation that the oldest cells of the organ of Corti appear at the apex and the youngest at the base suggests a hypothesis concerning the growth of the cochlear duct. In the twelve day mouse embryo the cochlear duct is a small out pocketing from the region of the otic vesicle which will eventually become the saccule (58) This small appendix grows and spirals until the mature form of the cochlea is obtained. The observations that the older hair cells were at the apex would suggest that the growth area might be at the junction of the cochlear duct and the primitive saccule. Growth by cell division at this point would cause the apex, with its already divided cells, to move away from the saccule. The spiral ganglion cells appear not to take part in this growth pattern but follow their own pattern so that the oldest spiral ganglion cells deploy themselves at the basal portion of the modiolus and the youngest at the apical portion. In the mature cochlea the oldest cells of the organ of Corti are nearest the youngest cells of the spiral ganglion, and vice versa

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PROBABLE MECHANISMS UNDERLYING KERNICTERIC HEARING LOSS

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CONTENTS

ABSTRACT

This paper discusses the hypothesis that the hearing losses which sometimes result from kernicterus are 1) caused by lesions within the cochlear nuclei and 2) that these lesions disrupt transmission of tonotopic (place) information more radically than they do analysis of time-locked (volley) information. The paper first considers the nature of kernicteric lesions. It then describes the audiometric impairment characterizing kernicteric hearing loss. The typical contour is a plateau of mild impairment (circa 30 dB ISO) from 250 cps downward, a second plateau of substantial loss (circa 75 dB ISO) from 2000 cps upward, and a fairly smooth transition between these two. Next, the paper reviews the psychoacoustic evidence that there is a volley-sensitive mechanism as revealed by the experiments on "periodicity pitch". Periodicity pitch experiences are most prominent when stimuli fluctuate less than 300 times per second and they grade to non-existence by 2000 times per second. Finally, the paper reviews the electrophysiological studies of response of individual neurons within the auditory nerve and cochlear nuclei. These studies demonstrate that neural elements are arranged in tonotopic arrays. However, as judged by the distributions of characteristic frequencies encountered in these experiments, this tonotopic representation is richest for frequencies above 1000 cps and is very sparse for frequencies below 300 cps, a fact that argues against analysis on the basis of place for low frequencies. Concurrently, moreover, the neurons with the lower characteristic frequencies show time-locking (volleying) in their responses. This time-locked information would seem to be the primary type available for frequencies below 300 cps; place information would seem to be the primary type available at high frequencies, but both types would seem to be generated in the intervening range. These several considerations support the opinion that kernicteric hearing loss is the manifestation of damage within the cochlear nuclei and that the most radical effect of this damage is to disrupt the place-sensitive mechanism while leaving the volley-sensitive mechanism relatively unimpaired.

There are as Goodhill (in press) has recently reviewed for us contradictions as to the degrees and incidences of lesions produced in the cochlear nuclei by kernicterus. Views run the gamut from that of Crabtree and Gerrard (1950) who contend that kernicteric lesions occurring in the dorsal and ventral cochlear nuclei produce hearing loss to the opinion of Haymaker *et al.* (1961) who feel that the afferent auditory system is almost always spared by kernicterus.[1] The first opinion is supported in one way or another by Barr and Klockhoff (1959) Fisch (1955) Goodhill (1950 1956 1957) Gerrard (1952) Perlstein (1961) Hardy (1961) Ruben (1964) and Newby (1964) By contrast Benitez *et al* (1966) Blakeley (1959) Dublin (1951) Flottorp *et al* (195) Kelemen (1956) Malamud (1961) Markle and Miller (1963) Matkin (1965) and Myklebust (1956) are among those who either imply or contend that whatever hearing loss occurs because of kernicterus is the result of peripheral (inner ear) lesions and that the central auditory effects of kernicterus, when they occur are manifest by imperceptions rather than true diminution in threshold acuity A third group including Rosen (1956) and Flower *et al* (1966) is content to describe symptomatology without commitment to a particular site of lesion Kelemen (1956) has presented the only histological observation suggesting that erythroblastosis fetalis can produce inner ear lesion. This evidence is somewhat tenuous since he found only that the cochlear and vestibular sacs are displaced Wolff according to Goodhill (in press) found in three cases some cytoplasmic changes in the spiral ganglion but normal end organ structures while Crabtree and Gerrard (1950) found the organ of Corti and auditory nerve normal in the one case whose temporal bone they examined

Despite the contradictions in the available data, it is justifiable to conclude that kernicteric lesions on occasion may center in the cochlear nuclei and in subsequent stages of the afferent auditory system These lesions are probably characterized by relatively diffuse reduction in nerve cell count.

[1] Kernicterus produces man lesions within the central nervous system in addition t whatever damage may be done within the uditory system, either in the cochlear nclei or t higher lev ls. Various thors, includi g Haymaker *et al* ha eported on xtra-auditory lesions and on non-auditory sequela t kernicterus. Clearl there are ma stances which the uditory ystem is pared major damage but these in t nces are of the topic of our discus ion.

Good post mortem evidence from cases where hearing loss w recorded is missing nce such cases have not come to utopsy but the conclusion that cell count i reduced arranted if one may extrapolat from bserv tions on infant who died soon fter birth beca se of kernicterus

Lesions of this type i.e., permanent widespread damage in the form of neuron depopulation, will have only chronic after-effects This type of lesion is clearly different from the more acute and later appearing pathologies of the cochlear nuclei resulting from cerebellopontine angle tumor vascular abnormality viral disease or intrinsic neoplasm. These other conditions may be expected to produce auditory symptoms quite different from those due to very early reduction in neuron density Consequently one is not warranted in reasoning that kernicterus does not produce lesions in the cochlear nuclei and in adjacent segments of the afferent auditory system because its manifestations are unlike those resulting from later appearing acute lesions in these same regions.

Recognizing that kernicteric damage is one of neuron depopulation we still do not know whether particular types of neurons are specially vulnerable and in consequence whether some kinds of neuronal network and synaptic architecture are more drastically disturbed by reduction in the density of neural units than are others. Neither do we know whether some of the functions that occur within the cochlear nuclei are more susceptible to impairment than others even if particular types of neurons are not more prone to destruction from kernicterus. These are matters which await exploration Meanwhile, however there is support for the belief that kernicterus sometimes damages the cochlear nuclei substantially Moreover the audiometric configuration typifying kernicteric hearing loss suggests the probability that when such damage occurs a differential disturbance in function results

THE CHARACTERISTIC AUDIOMETRIC CONFIGURATION

The hearing losses that result from kernicterus tend to fit a characteristic audiometric pattern This pattern is exemplified by Table 1 which presents data from five American studies. Note that the five investigations it reports show relatively similar central tendencies. Loss was mild for low frequencies, circa 30 dB at 250 cps, but then graded to about 70 dB at 2000 cps and 75 dB at 4000 cps

Matkin's (1965) data, which are discussed more fully later in this paper exemplify this configuration well (See Figure 1) His 22 subjects yielded an average loss for 125 and 250 cps combined of 31 7 dB, while the mean loss for 2000 and 4000 cps combined was 77.2 dB. The mean difference between these two levels was 45.5 dB. As can be seen from Table 2, this transition involved the following mean shifts per octave 16 4 dB drop in acuity between 250 and 500 cps, 16 6 dB between 500 and 1000 cps, and 8.3 dB between 1000 and 2000 cps. Thus, the major change in acuity level occurred in the two octaves that lie between 250 and 1000 cps, with almost the same amount in each.

The picture just described namely one where frequencies from 250 cps downward exhibit slight loss while those from 2000 cps upward show marked loss may be viewed as resulting from differential damage to two distinct mechanisms underlying auditory acuity According to this interpretation one mechanism, which serves low frequencies, has here been less disturbed than has the others mechanism, which serves high tones while the transition in hearing levels in the mid frequencies is interpreted as evidence of progressive shift from dependence on the low frequency mechanism to the high frequency one

It is very difficult to reconcile this concept of differential disturbance in acuity with the idea that the kernicteric lesion is cochlear The inner ear does not possess two mechanisms for auditory acuity that operate over dissimilar segments of the frequency range. Instead it demonstrates the tonotopic patterning of mechanical analysis that Békésy (1960) has described Thus, if one attributes the configuration of the kernicteric audiogram to cochlear lesions he must assume that kernicterus produces more damage at some points along the cochlear partition than at others. This assumption of subtle geographic difference in end-organ susceptibility to damage becomes untenable 1) when one remembers that there is no evidence of any invasion of the cochlea by bilirubin, which is the substance that is deposited at points of kernicteric lesion, and 2) when one remembers that

whatever anoxic influence might arise within the inner ear in consequence of the kernicteric syndrome must be relatively generalized In other words, the temporary and diffuse neo-natal pathology which the kernicteric under goes is most unlikely to produce the distribution of damage to hair cells and/or primary neurons serving particular frequencies that would be necessary to cause the kernicteric configuration of hearing loss on a peri pheral basis.

The more reasonable alternative is to conclude that the kernicteric dam age occurs more centrally specifically at a location where two clearly distinctive mechanisms for auditory acuity are operative yet low enough in the auditory system so that hearing loss *per se* emerges as a primary symptom. The cochlear nuclei appear to satisfy these requirements. They have been found to be susceptible to kernicteric damage and they constitute the first auditory way-station having sufficient complexity to allow multiple and differential processing of incoming neural information

A word should be said now about the two mechanisms involved The premise being supported in the present paper is that these are 1) the volley sensitive mechanism serving low frequencies and 2) the place-sensi tive mechanism serving high frequencies. *The hypothesis under considera* tion at the moment is that the audiogram characteristic of kernicteric hearing loss results from greater impairment in the functioning of the place-sensitive mechanism

The concepts as to how differential involvement of these two mechanisms could produce the kernicteric audiogram are illustrated in Figure 2 Parameters for this illustration are arbitrary but they were chosen to yield a configuration conforming closely to the median audiogram for Matkin s group of kernicterics. Here the volley sensitive mechanism is envisioned as operating alone from 300 cps downward and as being impaired about 30 dB (ISO 1964) The place-sensitive mechanism is envisioned as having primary sway from 1300 cps upward and as exhibiting about 75 dB loss. Because the loss for place sensitivity is much greater than for volley sen itivity the latter is also presumed to operate within the transitional region from 300 to 1300 cps, but hearing becomes progressively poorer as frequency in creases because the volley sensitive mechanism declines progressively in efficiency above about 300 cps. The place-sensitive mechanism is presumed to take over when the kernicteric damage to volley sensitivity coupled with the inherent decline in volley sensing efficiency cumulate to more loss than the impairment imposed on the place mechanism Thereafter the place-sensitive mechanism determines efficiency Figure 2 depicts this take-over as occurring near 1300 cps and involving hearing levels of about 75 dB It should be reemphasized that these values, as with the remainder of Figure 2 were obtained by schematizing Matkin s median audiogram and not by any preconception regarding what the values might be

Among questions which are critical to the foregoing hypothesis are the ones as to 1) whether the volley-sensitive mechanism does in fact operate

2) if so, whether it holds supremacy from 250–300 cps downward and 3) if so whether it gives way fully to the place-sensitive mechanism near 1300 cps

Two types of evidence that bear on these questions and that support the underlying hypothesis are reviewed later in this paper These evidences consist of the psychoacoustic findings on "periodicity pitch" and the data from electrophysiological investigations on behavior of single neurons within the auditory nerve and the cochlear nuclei. Before considering these evidences however we must evaluate the variability of impairments exhibited by patients with kernicteric hearing loss

Substantial differences in both the configurations and the degrees of individual losses were encountered during the studies listed in Table 1 The variability is even greater when one includes the data obtained by Byers *et al* (1965) Crabtree and Gerrard (1950) Fisch (1955) Goodhill (1950 1957) and Keaster (1966)

Discrepancies among studies have arisen because criteria both for case selection and for measurement of hearing have differed widely Investigators have not sampled identical populations in a uniform manner Crabtree and Gerrard (1950) for example, report on patients ranging from 4 to 23 years in chronological age, whereas Matkin (1965) required that each of his 22 subjects have a mental age of at least eight years Again, Byers *et al.* (1965) included several young cases who showed loss by voluntary audiometry but had normal hearing by electrodermal audiometry while each of Matkin s subjects exhibited about the same loss by EDR as by conventional audiometry

After allowing for such factors, the residual variations in kernicteric hearing loss may be attributed to differences in the lesions kernicterus produces from one person to the next It thus becomes pertinent to examine the distribution of audiometric contours encountered among such patients as a gauge to the homogeneities and disparities in the physiological damages they have suffered Here in view of the discrepancies among past studies,

TABLE 1 *Central tendencies of pure tone thresholds exhibited by samples of patients with hearing losses due to kernicterus*

V lues for Bl k ley extracted from published audiogram Medians for Flower *et al* computed by present writer Matkin 1 data gleaned by him from the clinic files at Northwestern University Matkin 2 data obtained directly by him n second population. All thresholds shown i dB re ISO 1964 norms.

Investigator	No. Cases	Test Frequency 125	250	500	1000	2000	4000	8000
Blakeley[a]	20	—	30.0	42.0	55.0	65.5	74.0	81.5
Flower *et al*[b]	15	—	32.5	40.5	60.5	65.0	79 7	—
Hardy	26	—	33.2	38 1	45.7	53.8	56.1	—
Matkin 1	40	29 0	33.0	45.0	63.0	70.5	74.0	74.5
Matkin 2[a]	22	29.3	31.8	40.3	65.4	6.6	77.5	73.5

Mean Median

Act olo-l g g S ppl 221

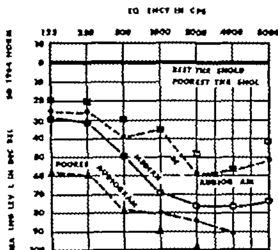


FIG. 1 Resume of Matki   udiometric data for 22 subjects with kernicteric hearing loss.

one must decide which set of results is probably most typical of kernicteric hearing loss uncomplicated by auditory imperception, by motor incoordina tion or perceptual disorder that would contaminate response or by unrelated variables such as coincidental conductive loss. Matkin s (1960) data seem particularly free from such contamination Hence the writer has chosen his group as being representative and cohesive for the purpose at hand.

Matkin s pertinent findings are summarized in Figure 1 [3] Here one sees, in addition to the median audiogram already mentioned the audiogram for the best single ear and the poorest single ear within the group Also, the total range of loss at each frequency is depicted in terms of the two extreme thresholds at that frequency Interestingly the best single audiogram comes close to depicting the least loss found within the group from 1000 cps upward while the poorest audiogram represented the worst performance within the group at all frequencies below 1000 cps.

Examination of individual records reveals that every subject had a con figuration of greater high frequency loss than low frequency loss. Moreover most low frequency thresholds clustered in the region of the best per formance for the group indicating that the losses in this tonal range were relatively homogeneous The distribution around the median was less skewed at high frequencies, bespeaking less consistency in this latter range

Further insight into the variations around the group pattern can be derived by analyzing individual audiograms to ascertain the octave within each where the greatest change in threshold level occurred. Results of such analysis are included in Table 2. Note first (Row 2 of the table) that in thirty-seven out of fifty-one instances the maximum increase in loss per

Matk   obtained his thresholds with an audiometer calibrated to the ASA 1951 norm. All statistics reported in this paper were computed sing hl ASA 1951 thresholds, but ll hearing lev ls re being reported here re the ISO 1964 norm.

TABLE 2 *Mean increase in hearing loss per octave reported in octaves between 250 and 4000 cps exhibited by Matkin's 22 cases (44 ears) with pure tone loss due to Kernicterus (1965)*

Results shown for entire group combined and for two subdi isions of the group, o consisting of those subjects howing their maximum hift in th octave in question nd the other consisting of subject showing the maximum shift in another octa e

	Octave[a]				
	125–250	250–500	500–1000	1000–2000	2000–4000
1 Mean increase (44 ears)	3.2 dB	18.4 dB	16.6 dB	8.3 dB	5.1 dB
2. Ears with maximum change in this octave[b]	0	14	23	11	3
3. Mean increase for only these ears[b]	—	25.1 dB	23.0 dB	21 7 dB	25.8 dB
4. Ears with maximum change in another octave	44	30	21	33	41
5. Mean increase for remaining ears	3.2 dB	12.0 dB	9.6 dB	4.1 dB	3 6 dB

[a] Th 4000–8000 cps oct ve i omitted because 18 instances of n response occurred at 8000 cps.

[b] In the seven instances where the maximum occurred in two octaves, data for those ears were veraged in both.

octave (or shift in threshold between adjacent test frequencies) occurred between 250 and 1000 cps Fourteen times the greatest change appeared in the 250–500 cps span and 23 times in the 500–1000 cps span. Note further that the mean value of the maximum change remained relatively stable irrespective of the octave involved. The overall average of the maxi mum shifts was 23.5 dB, while the values for successive octaves from 250–500 cps upward were 25 1 23.0 21 7 and 25.8 dB A further point of interest is that, combining data for all frequencies, only four instances occurred where the maximum intra-octave shift was as small as 15 dB and only seven where it was 35 dB or more The largest single shift was 45 dB. There were 13 instances each of shifts of 20 and 30 dB, and 14 instances of 25 dB ones Thus, the group showed reasonably good homogeneity in regard to the magnitude of the maximum intra-octave shift

One concludes that a primary characteristic of the typical kernicteric audiogram is a sharp break in hearing level averaging about 25 dB in a

single octave but occurring at different octaves for different individuals and sometimes at different octaves in the two ears of the same person

A provocative extension of the picture appears when one averages the remaining intra-octave increases in hearing loss, i.e. those increases where the maximum did not occur across the octave in question. The values which emerged appear in the fifth row of Table 2. The means for these residual data approximated 10 dB in each of the two octaves *immediately below* 1000 cps but only about 4 dB per octave above this frequency. The two relations which stand out are 1) that appreciable intraoctave increases occurred (on the average) in each octave between 250 and 1000 cps even when the maximum increase was in some other octave and 2) that the increase tended to be slight in each octave above 1000 cps unless the maximum change for that ear occurred in this octave.

Described in a slightly different way, Matkin's 22 subjects exhibited hearing losses that increased systematically across the range from 250 to 1000 cps irrespective of whether there was also substantial shift between 1000 and 2000 cps. Not a single ear was tested wherein the threshold was not worsened by at least 10 dB in the 250–1000 cps span. Moreover, when considering shifts within a single octave there was never an instance in this range where the threshold for the higher frequency was the better of the two tones bracketing the octave, and there were only four instances (out of 88 possibilities) where the threshold was the same for two adjacent test tones.

Moving to the overall generalization, it is apparent that the individual variations in kernicteric hearing loss, as exemplified by Matkin's data, are variations around a pattern of loss typified by a plateau of relatively good hearing for low frequencies followed by a transition to a plateau of relatively poor acuity for high frequencies and characterized by a particularly sharp change in hearing level across one of the octaves between 250 and 4000 cps.

Turning to the question as to what variations in kernicteric lesion are implied by the individual differences that Matkin observed, it is obvious that we lack information which would allow designation of the anatomical details of damage. But we may consider the issue in terms of the ways in which the efficiencies of the volley-sensitive and the place-sensitive mechanism seem to have been modified from subject to subject.

Since, as is clarified later in this paper, the volley-sensitive mechanism takes precedence for frequencies from about 300 cps downward, the relative homogeneity of subject responses that was observed in this range would imply that the volley-sensitive mechanism tends to be rather uniformly disturbed from person to person, provided it is impaired at all, by a kernic-

It should be mentioned here that analyses of other populations, such as those studied by Blakeley (1959), Flower et al. (1966) or Kessler (1966) lead to essentially the same generalization.

teric lesion However the occurrence of a few subjects with moderate loss for low frequencies indicates that volley sensitivity can be disrupted in varying degrees

In those instances where a sharp break in hearing level occurred between 250 and 500 cps, that is, where Matkin s median audiogram represents approximately the individual s response, one may presume that the place-sensitive mechanism was substantially disrupted across its total range so that a situation akin to the one depicted in Figure 2 existed However this interpretation can not be extended without modification to cover those cases where hearing remained fairly good to 500 or 1000 cps and then exhibited its sharp break toward greater loss These latter are circumstances where one must assume that the place-sensitive mechanism was severely disrupted only in its higher range One conclusion to be reached *from these facts is that the place-sensitive mechanism is subject to much greater variability of disruption than is the volley sensitive mechanism*[*] This situation would account not only for the individual differences which Matkin s subjects revealed in the octave wherein their sharp break occurred but also for the reduced homogeneity of loss at higher frequencies that characterized the group The second conclusion to be reached is that those segments of the place-sensitive mechanism serving the higher frequencies are the more generally susceptible to kernicteric damage since all cases showed substantial loss for these tones.

The concept that the place-sensitive mechanism is susceptible to differential damage even though the lesion is not cochlear is reasonable when one remembers the tonotopic system(s) within the cochlear nuclei If one *may draw the analogy from electrophysiological findings on cats* (Kiang 1963 Rose 1960) there are at least three tonotopic maps" at this level Thus, place-sensitivity by virtue of the fact that it is spatially distributed here should be responsive to geographic differences among lesions, and appropriately restricted lesions should have limited frequency effects We *must remember that, in contrast to the situation to be expected for the* cochlea differences in kernicteric lesion do occur in the central nervous system Here then, the vehicle for variability in symtomatology is at hand

At this point one must ask why the entire kernicteric audiogram can not be attributed to differential involvement of the central tonotopic mechanism If the explanation just given is applicable to the higher audiometric frequencies, should it not also be responsible for losses in acuity at low frequencies? The answer if we may anticipate here a conclusion that is developed later in this paper and that derives from electrophysiological data is that tonotopic mechanisms do not adequately cover frequencies below about 300 cps. These frequencies are very poorly represented tonotopically either in the auditory nerve or in the cochlear nuclei Hence damage

One evid nc th t there i ari bility i damage t th place-sensitive mechanism i found i th fact that some kernicteric udiograms show improved acuity re 2000 and 4000 cps t 8000 cps, whil there do not.

to tonotopic systems within the cochlear nuclei should not have the same effect on these frequencies as on higher ones.

A further point must be stressed. One would not expect the volley-sensitive mechanism to be as susceptible to differences among lesions within the cochlear nuclei as is the place-sensitive mechanism, since no specific loci for volley sensitivity have been identified and since the neurophysiological substratum for this mechanism is probably diffusely distributed rather than neatly mapped. However, the reason for presuming that the volley-sensitive mechanism is the less susceptible of the two to kernicteric damage is not that it may have more diffuse representation within the cochlear nuclei. The reason for this opinion derives 1) from the observed shapes and variabilities of kernicteric audiograms and 2) from recognition that low frequency hearing is served by the volley-sensitive mechanism. Had the audiometric relations been reversed one would have needed to reason that the tonotopic mechanism is the more resistant to kernicteric damage.

Of course the foregoing point of view is tenable only if it can be demonstrated that a volley-sensitive mechanism which must perforce be a central mechanism, exists. One major array of evidence pointing to the reality of the volley sensitive system is found in the psychoacoustic data on "periodicity pitch" Specifically several kinds of experiment have demonstrated that a form of frequency discrimination or pitch experience, can be achieved by periodic, low frequency fluctuation of sound under circumstances where excitation either is restricted to regions of the cochlea serving high frequencies or is uniformly distributed within the cochlea. These experiments show that low pitched" experiences can result without differential excitation of the sensorineural system situated along the low frequency area of the basilar membrane that is, without inciting the greatest disturbance at the low frequency end of the cochlear partition

One type of research has employed modulated noise The first major study in this category was performed by Miller and Taylor (1948) They investigated the ability of normal listeners to respond to interruptions imposed in white noise. They used a sound time fraction of 0.5 Since their modulated signal maintained the same spectrum as uninterrupted noise the place mechanism could not have been serving as the basis for whatever identification of interruption rate their subjects revealed These subjects achieved a pitch experience which was sufficiently definitive from approximately 40 to 250 interruptions per second to allow its being matched to the pitch of a sinusoid. A less precise discrimination occurred between about 250 and 2000 cps. Here subjects noted a qualitative difference between steady and interrupted noise without being able to make a pitch match At still higher frequencies even this distinction disappeared. Miller and Taylor interpreted their findings in a manner supporting the volley principle when they wrote, "Presumably the ability to perceive interruptions in a random noise depends upon the synchronous firing of the fibers of the auditory nerve"

Harris (1963) had normal hearing subjects match gated white noise to trains of 0 1 msec clicks rather than to sinusoids He found that matching could be performed using either broad band or 2400 cps high pass noise at gating rates up to 750 interruptions per second while a weak timing signal up to about 2000 interruptions per second was apparently perceived when 4800 cps high pass noise was being gated Another important observation was that a lateralizable image of the gated noise was observable up to about 600 interruptions per second We see again that differential per

ception of the frequency of interruption can occur as long as interruption rates are low even when the stimulus is one that causes equally distributed cochlear disturbances

Nieder and Creelman (1963) found that when they combined interrupted noise in one ear with correlated but continuous noise in the other ear a lateralizable image resulted. This image had the same pitch and tonal quality as when chopped noise was administered to one ear alone The apparent position of the binaurally induced image shifted as intensity relations between ears were modified Nieder and Creelman feel that their findings support the existence of a central mechanism for perception of periodic pitch. They state It is hard to see how the central periodic pitch found in these stimulus situations can be ascribed to localized activity of restricted low-tone areas of the basilar membrane. If there were such activity set up by the chopped-noise signal it would seem that it would be relatively independent of the fine structure of the noise bursts and hence that localization in auditory space also would not be influenced differentially by correlated as opposed to uncorrelated noise."

Cramer and Huggins (1958) report on a related phenomenon which carries similar implications Noise was presented from one source so that it was the same in both ears except for a small band or segment, which was out of phase in the two signals Listeners heard a faint tone deep in a noisy background The pitch of this tone depended upon the frequency range within which the pitch shift was being generated, but tonality appeared only so long as this range remained below about 1400 cps This experiment like the one by Nieder and Creelman, clearly implies that the analysis of time-locked information occurs subsequent to the inner ear and auditory nerve Licklider (1962) in commenting on the Cramer Huggins phenomenon, notes that it poses an embarrassing problem for classical place theory He remarks that the theory " says nothing about binaural interaction and here is a controllable low pitch arising through binaural interaction from stimuli that monaurally are nothing but random noise"

Another kind of experiment supports the premise that a low frequency volley-sensitive mechanism exists This approach utilizes pips of high frequency sound to achieve a low pitch experience Here only high frequency components are present in the stimulus itself but the auditory perception implies otherwise

In one of these experiments, Davis, Silverman and McAuliffe (1951) produced 90 to 150 tone pips per second by delivering rectangular pulses through two filters set with high and low cut-offs at 2000 cps. Nearly all the acoustic energy in the resultant stimulus was in an octave band centered at 2000 cps The resultant sound was a "metallic buzz" which was not the same as the pitch experience produced by a low frequency sinusoid but which was perceived to have pitch as soon as pip frequency was varied. The study was designated to test the theory that pitch is determined by volleys below 1000 cps Davis and his associates conclude, "The psycho-

physical correlates may prove to be quite complicated. For example *frequencies* above 4000 cps (and probably all available frequencies) are translated in the ear into *position* i.e., to *choice of channel* but below 800 cps (and perhaps, by the volley principle up to 4000 cps) information as to frequency is also carried in the form of *time-intervals between impulses* Pure tones set up a *particular* relation between these two types of information but a series of tone-pips gives a very different relation "

Thurlow and Small (1955) performed a somewhat different experiment in that they pulsed a sinusoid carrier frequency directly rather than achieving a spectrum of limited frequency range through filtering They used one of two carrier frequencies, either 1000 or 5000 cps The carrier frequency was interrupted 100 times per second but spectral energy was concentrated around the carrier frequency rather than the interruption rate. When the carrier frequency being used was 1000 cps, subjects heard only a low pitch attributable to the pulsing rate even though much more energy was centered at the carrier frequency and auditory sensitivity is keener at 1000 cps than at 100 cps The same low pitched experience persisted when the carrier frequency was 5000 cps, but now a high pitched tone was heard concurrently A noteworthy fact was that noise capable of masking a 100 cps sinusoid did not obliterate perception of the low pitch. That is, this noise did not mask either the 5000 cps carrier which it would not be expected to obscure nor the low frequency information generated by pulsing the carrier This observation demonstrates that the periodicity pitch experience can not be attributed to a low frequency place mechanism In discussing their results, Thurlow and Small state "A complete theory of pitch matching will obviously have to include more than sensory input mechanisms

We would favor a neural sorting process by which successive volleys of impulses in the auditory nerve cause activity in specific places in a higher center (probably cochlear nucleus) depending on the time intervals between volleys and on the characteristics of the neural sorting mechanism." *They feel this sorting mechanism must be quite complex and must include* both excitatory and inhibitory components

Small and Campbell (1961) performed a further study on the masking of a pulsed carrier tone. They interrupted a 2200 cps tone 150 times per second The result was a low pitch corresponding to a 150 cps pure tone This low pitch experience could be obliterated by the same level and spectrum of noise required to mask the carrier when the latter was presented continuously whereas the low frequency band of noise which would mask a 150 cps sinusoid did not eliminate the experience Thus in terms of the place mechanism the low pitch was hallucinatory to the extent that the cochlear vibrational pattern ordinarily associated with the low frequency was not for the moment present, and hence was unmaskable by the low frequency noise Small and Campbell state "If masking is viewed as a neural phenomenon these data provide additional evidence of the neural nature of periodic pitch " They conclude that rather narrow band filtering

in the frequency domain precedes temporal analysis of the stimulus wave form by the auditory system, and they state " If 'traditional filtering' in a masking situation is a result of cochlear mechanical action and lower order neural activity then this would place the temporal analyzing mechanism central to " this lower order neural activity

Small and McClellan (1963) performed a somewhat different experiment which fits into the same overall picture namely that there is a mechanism for response to time-locked information which yields pitch experience They varied the time delay between members of pulse pairs The resultant pitch corresponded to the reciprocal of the time delay Small and McClellan feel this phenomenon is not well accounted for by traditional place theory

The final major area of psychoacoustical experimentation favoring periodicity pitch deals with the "residue phenomenon" Licklider (1959) considers this phenomenon one of the primary evidences that peripheral (inner ear) frequency analysis can not alone account for our ability to differentiate among stimulus frequencies

Schouten (1963) has been a leader in investigating the residue phenomenon He describes it as " the joint perception of a number of neighboring Fourier-components of the sound as a single percept of sharp timbre and more or less low pitch It occurs when the Fourier-components are too narrowly spaced for them to be resolved and perceived separately The pitch if present is roughly equal to the spacing of the components Typically for example three neighboring harmonics of about 2000 cps that are separated by intervals of 200 cps generate an experience of a 200 cps pitch This type of low pitch is achievable with clusters of high frequency harmonics up to about 5000 cps Schouten has shown that a variety of parameters affect the limiting frequencies of the residue and a most critical point is that *the residue phenomenon appears at sufficiently low intensities so that one can be sure that there are not products of mechanical distortion which are introducing artifacts*

Licklider (1962) emphasizes that the low subjective pitch of the residue phenomenon persists even though the low frequency channels of the peripheral sensorineural system are saturated with random masking noise "Thus," he points out, "in direct contradiction to pure place theory a low pitch may be heard through high frequency cochlear channels " Along somewhat the same line Schouten says the phenomenon supports the supposition that each area of the basilar membrane may give rise to sensations of widely different pitch, depending upon the pattern of stimulation He postulates pitch extraction and sharpening processes, which he says determine the pitch of the stimulated area and which are both probably the product of neural interactions Ritsma (1962) who has also studied the residue problem extensively expresses a similar view thus, "One may conclude that in themselves the components constituting the stimulus do not contribute to the resulting sensation of pitch One should rather interpret the time function of the stimulation in a particular area on the basilar

membrane as a decisive factor in bringing about a sensation of pitch." He stresses that the mechanism which underlies the residue phenomenon (Schouten's pitch extractors) operates only for lower frequencies, and he comments, "Although the location of the hypothetical pitch extractors is as yet unknown, nevertheless it must be posterior to the analyzing function of the basilar membrane . . ."

Plomp (1960) used a somewhat different experimental approach. He had subjects compare pitch of a complex tone with the same complex modified in two ways. First, the frequency of the fundamental (and in selected instances of the next few harmonics) was reduced by 10%. Second, the remaining overtones were simultaneously raised by 10 percent. The fundamental frequencies he used were 125, 175, 250, 350, 500, 700, 1000, 1400 and 2000 cps. Plomp reasoned that if the pitch of the complex tone was based on the frequency of the fundamental it would seem to be lower after the complex had been modified, whereas it would seem to be higher if pitch depended on periodicity captured in the new relation among the harmonics. The latter experience occurred uniformly enough except at 2000 cps so that Plomp concluded that periodicity of the harmonics rather than frequency of the fundamental operates from 1400 cps downward. He sees no conflict between this mechanism and the filter band characteristic of the ear, saying, ". . . the frequency separation of the harmonics of complex tones below about 1400 cps is small enough to allow the periodicity of the sound wave to be retained in the output signals of many cochlear filters. Apparently all these filters together give rise to a stronger pitch sensation than the filters passed by only one of the lower harmonics."

In this connection, it is interesting to note the conclusion which Flanagan and Guttman (1960) reached when they studied the pitch of periodic pulses and evaluated their findings by also studying responses to pulses of an electrical analogue of the cochlea. They reasoned that there are two pitch modes manifested at the level of the basilar membrane, saying, "The first mode, in which pitch assignments equal to pulse rate are made, occurs when the repetition rate is low enough for successive pulses to be resolved in time over the length of the basilar membrane. The second mode, in which pitch assignments equal to fundamental frequency are made, occurs when the frequency is high enough for the fundamental component to be resolved in frequency by the membrane."

The several experiments described above, dealing with various aspects of periodicity pitch, point to the probable existence of a mechanism central to the cochlea which is responsive to information in the time domain.

Licklider has developed detailed theories embodying this concept. He proposes that there are two processes which operate in the analysis of frequencies of sound stimuli. One process consists of the traditional place mechanism, while the second involves non-cochlear analysis in the time domain. Licklider's (1959) triplex theory postulates a system whereby time delays between successive neural discharges are translated into a geographic

pattern characterized by excitation of specific and distinctive neural units within the brain stem. According to this theory incoming periodicity information (volleys) is transformed by a central mechanism into appropriate differences in place of neural activity. Licklider (1962) extended his views by cataloguing the various transformation systems whereby incoming temporal information might be allocated to specific neural locations. He emerged with the view that Property filters have high versatility. They are, Licklider tells us, "... filters in a very generalized sense—each one selectively responding to one or more spatio-temporal patterns of incident excitation ... Each unit would recognize the presence of a particular property of the stimulus." Properties might include sensitivity to specific clicks, trills and glissandi, etc. Some filters certainly could be elements responsive to particular periodicities, i.e. each acting as a unit tuned to its respective periodicity. The critical consideration from our standpoint is not, however, whether the Property-filter model is the most applicable of Licklider's formulations. The critical consideration is that Licklider has given us extensive and ample arguments favoring the view that a central mechanism for periodicity discrimination must exist concurrently with a peripherally based place mechanism. Moreover in this regard it is particularly pertinent to note Licklider's remark that, "The periodicity-to-place transformation ... should probably be associated with an extended segment of the afferent pathways, starting with the cochlear nuclei."

The views of Tonndorf (1962) and of Békésy (1960, 1963) are counter to the foregoing interpretation. Tonndorf concludes on the basis of his work with models that a cochlear system in which stiffness varies with distance along the cochlear partition produces demodulation of modulated signals which allows detection of temporal properties in such signals on the basis of place patterns they induce along the cochlear partition. These patterns allow a time/frequency analysis in the sense of Gabor. Tonndorf says, "The concept of cochlear function presented here is no longer based upon the notion that the cochlea executes an exclusive Fourier analysis with respect to all applied signals. It rather suggests a time/frequency analysis. Since it is still based on the assumption that this analysis results primarily in a place representation it may be considered a *modified place concept.*" Tonndorf finds psychoacoustic support for this view in Voots (1962) work, which Tonndorf says supports the opinion "... that the frequency corresponding to the periodicity pitch is represented within the cochlea independent of the high frequency complex of the pulsed signal used."

Békésy (1963) in commenting on the periodicity theory as formulated by Schouten and Licklider states, "The periodicity theory has no difficulties in the lower frequency range but it encounters some problems in higher

A interesting feat re of Licklider' Property filter hypothesis is that it is pplicable t the central process ing f place } form tion from the cochlea as well as of periodicit f formation.

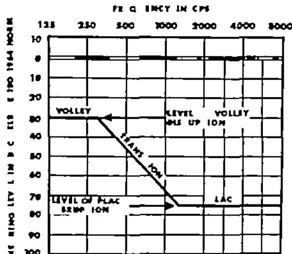


FIG. 2. Schematized illustrati f the hypothesis that mild impairment f v lley mech nism nd substantial impairment f place mechanism produces audi metric configuration such as is most characteristic f kernicteric heari g l ss.

frequencies" Békésy finds some contradiction in Schouten s results, i e up to 200 cps the residue is one octave too high Such considerations lead him to conclude that the periodicity principle alone is not sufficient to account for the pitch of complex sounds" Moreover Békésy explains the Cramer Huggins phenomenon on the basis of the place theory He feels the place theory is able to derive connections among many phenomena of hearing, in addition to providing a theory of pitch." However he also believes " both place and periodicity theories of hearing should be pur sued further since in this process new questions are raised which will help us to go from the cochlea to the higher neural levels"

Obviously the present paper is not going to resolve the controversy between Békésy s views on periodicity pitch and those of Licklider A great deal of experimentation such as Békésy advocates is required to settle all the issues However the evidence seems fairly clear cut on the questions which are paramount here. The phenomenon of periodicity pitch is recog nized by all as existing. Our concern is whether *the analyzing mechanism* that underlies the periodicity pitch phenomenon is in *any* important sense a central phenomenon, that is, whether in *any* sense the central decoding of time locked information is involved. If such is the case even though there also turn out to be peripheral aspects to the analytic activity our thinking must allow for two separate processes and the distinction between them requires the operation of central mechanisms.

Among the features which the aforementioned experiments on periodicity pitch have revealed are three facts which seem to the present writer to *offer very convincing indirect evidence for the existence of a central volley* sensitive process For one thing, periodicity pitch takes precedence over carrier frequency pitch (so that only the former is heard) if periodicity

rates are low and carrier rates are only moderately high (1000 cps as contrasted with 5000 cps) Even when carrier frequencies are high, periodicity pitch persists although the pitch of the carrier frequency is now also noted. Secondly masking of periodicity pitch is achieved much more effectively by a masking spectrum centered around the carrier frequency than around the periodicity frequency Lastly the periodicity phenomenon is susceptible to binaural interactions which implies central analysis of temporal differences between the two incoming trains of neural information.

Finally it must be noted that periodicity pitch exhibits two other features which, in a sense, parallel provocatively the characteristics of the typical audiogram of kernicteric hearing loss as exemplified by Matkin's data. In the first place periodicities below about 300 cps produce the most definite and matchable pitch experiences when either white noise is gated or high frequency tones are pulsed The characteristic kernicteric audiogram shows a plateau of minimal loss from 250 cycles downward (See Figure 1) Furthermore, pitch experience becomes progressively less definite as the periodicity rate increases from about 300 cycles to somewhere between 1000 and 2000 cps The kernicteric audiogram shows its sharp transition of increasing loss across this same range These two characteristics of periodicity pitch (i.e., range of maximum definitiveness and range of decreasing clarity) parallel very closely the range of presumed action of only the volley mechanism and of transition to the place mechanism illustrated in Figure 2. One concludes that the picture of a volley-sensitive mechanism which emerges from experiments on periodicity pitch is in close agreement with the picture of this mechanism one may postulate from the hearing loss curves of kernicterus.

PLACE AND VOLLEY PLACE THEORIES

Békésy's (1960) extensive experimentation 1) on mechanical vibration of the cochlear partition 2) on the parallelism between the vibratory and the auditory senses, and 3) on phenomena of inhibition funnelling and sharpening seem at first impact to be in overwhelming support of the place theory His work has made it completely clear that extensive mechanical differentiation of acoustic spectra occurs in the form of spatial patterning of vibration along the cochlear partition Even though this patterning consists of relatively broad amplitude maxima so that *frequency differentiation* must be sharpened neurologically the interpretation usually given to his findings is that the place separation within the cochlea is sufficiently precise in the inner ear so that tonotopic packaging and tonotopic relaying is the prime process in the various neural stages of transmitting information in the frequency domain It is in this tradition that Davis (1962) when commenting on the work by Kiang *et al* (1962) on responses of individual auditory neurons, said, "The way in which the behavior of these units can be predicted from the known mechanical events, as described by Békésy and from the fundamental rules of behavior of nervous tissue is most satisfying and comforting The mechanisms of the inner ear include the concept of frequency analysis "

A major consideration arguing against a simple tonotopic theory is the fact that lower frequencies produce substantial spread of mechanical agitation on the basilar membrane This is one of the major considerations in Wever's (1949) volley place theory His estimates based on the cochlear damage produced by high level noise are that 40 per cent of the basilar membrane is heavily involved below 500 cps, 17 per cent at 2000 cps and still 5 per cent at 7000 cps In this connection we must recall the paradox that differential sensitivity to frequency change is particularly good at higher intensities and that spread of disturbance along the basilar membrane increases with rising intensities At higher intensity levels there can not be sharp boundaries to the areas of membrane agitation leading to excitation of only those neural elements serving highly restricted segments of the organ of Corti even with the aid of such peripheral sharpening mechanisms as 1) the changes in axis of displacement between tectorial and basilar membrane occurring where the travelling wave pattern has its maximum (Davis, 195) and 2) the neural functions of the inner ear which Békésy (1960) describes as setting up inhibitory effects and thus producing sharp localization of response

Békésy's concepts have been derived in substantial degree from his observations on the way in which inhibitory sharpening, summational and funnelling processes refine perception of vibratory stimuli applied to the skin. The point we must remember is that the refinements in sensation which these processes produce require interaction among at least several peripheral neurons and, hence, depend upon central processes that can not occur any more peripherally than the first complex of synaptic junctions. This consideration leads to the conclusion that there are central "networks", simple though they may be, which contribute refinements by reprocessing relatively gross information generated peripherally. These initial synaptic complexes are situated within the spinal cord for afferent innervation from most areas of the skin. Their auditory counterparts lie in the cochlear nuclei. Here there occurs the first central reprocessing of the information on spatial patterning generated at the cochlear level. One would thus expect the place-sensitive mechanism to be vulnerable to lesions in these nuclei.

Another consideration which a simple place theory disregards is the prospect that time-locked neural events may constitute primary information underlying pitch experience. This latter prospect is a foundation stone for Wever's volley place theory. He presents strong arguments for the view that only time locked neural information is useful at very low frequencies, with both time-locked and place information serving at intermediate frequencies. He recognizes the place mechanism as operating alone at high frequencies.

It is not important whether all the details of Wever's presentation are correct. The critical feature is his emphasis on the fact that over a wide frequency range the excitation of the individual unit in the acoustic nerve will occur at a particular phase of the stimulus. The end result as we should think of it here is a train of time-locked neural spikes which are decoded by the nervous system. As Kiang (1965) points out, impulses initiated by activity at the basal end of the cochlea will appear as synchronized volleys because this portion of the cochlear partition moves in phase. Impulses generated more apically will show varying delays that depend upon the phase differences which occur along the partition. The neural units carrying these latter impulses will not be discharging synchronously with neurons activated elsewhere along the cochlear partition, but they will preserve time locking within themselves. The central nervous system possesses the versatility to compensate for these systematic differences in delay and, hence, can undoubtedly decode timing information even though all units in the auditory nerve do not, strictly speaking, participate in synchronized volleying. That is, all of the useful time locked information travelling up the auditory nerve need not appear as volleys in the traditional sense.

The existence of time-locked information reaching the central nervous system offers the prospect that this information serves as a major substratum to a wide array of perceptions, not the least of which would be

perception of a stimulus as temporally orderly as a sinusoid. Thus, the demonstration that a certain degree of mechanical analysis occurs in the cochlea gives us information on the auditory mechanism s mechanical resolving power It is not proof that the concomitant ordering of neural events into time-locked sequences lacks critical importance as information requisite to perception within the frequency domain. Conversely of course the existence of time-locked neural sequences is not proof that the con comitant mechanical analysis within the inner ear lacks similar importance The point is that the auditory system appears to possess two mechanisms having different efficiencies at different frequencies It is this prospect which the traditional place theory disregards It is this view that Licklider has formalized in his triplex theory and his discussion of the Property filter concept. It is this duality which Klang (1965) recognized when he wrote after his extensive work on response of individual neural units, " a strict place theory appears to be untenable and Wever has reviewed the evidence for a second principle in pitch discrimination based on time patterns of the responding units It would appear that the psychophysical dimension of pitch which has been frequently thought to be unitary has at least two correlates at the auditory nerve level. It is the imposition of the single word pitch on the characteristic of frequency discrimination that obscures the fact that several basically different mechanisms operate within the organism."

Keidel (1963) in evaluating tuning between the central auditory path ways and the ear expressed the viewpoint of the present paper thus, one of the major problems of the physiology of hearing is to learn how the spatially organized frequency discrimination and the analysis of the time periodicity interact No one would claim the periodicity-analysis to be effective at very high frequencies or that the physical dispersion of frequencies within the cochlea provides effective separation at lower frequencies than approximately 300 cps Effects like the residue phenomenon can hardly be explained spatially when there is no more spatial differentia tion between a tone of 300 and any 100 cps within the cochlea Therefore the over lapping between those two systems of sound analysis in hearing (not in the ear) must be somewhere between 300 cps and maximally a few kilocycles Thus there should be some tuning between a spatially work ing system for frequency-discrimination and another one for periodicity analysis on the one hand and between the information processing parts of the CNS and the peripheral coding systems of the ear on the other hand"

From this point of view one may proceed to the conclusion that the central processing of time-locked sequences requires very different func tioning at the level of the cochlear nuclei and possibly also at higher levels, than is involved in the sharpening of peripherally generated tonotopic in formation

SINGLE NEURON RESPONSE

Experiments on the behavior of individual neural units within the auditory nerve and the cochlear nuclei have supplied data bearing on these matters, including the question as to the range of tones within which each of the two frequency sensitive mechanisms appears to function.

Tasaki (1954) studied responses in the auditory nerve of the guinea pig. He reported that when pure tones up to 2000 cps were used as stimuli, single fibers transmitted impulses that " tended to appear at approximately the same point in the cycle of the stimulating sound The interval between these spikes showed a tendency to be at some integral multiple of the period of the applied sound wave " Later Tasaki (1960) expressed the view that this type of synchrony occurred up to 3000 cps The feature of significance is that he demonstrated time-locking between incoming wave and spike-response in the individual neuron element within the auditory nerve and that this relation appeared over a broad range of low and middle frequencies

Tasaki also described the threshold frequency curves of individual units in the auditory nerve. These characteristic curves depict the change in range of frequency response resulting from change in stimulus level He found that units differ substantially in their thresholds However at lower intensities within its response potential, each unit was activated only by a limited range of frequencies. It was at the higher stimulus levels that the fiber showed reaction to more distant tones, with the spread in response extending primarily toward lower frequencies.

Katsuki (1962) and Katsuki *et al* (1962) working with monkeys, confirmed and extended Tasaki's observation on characteristic curves They also reported a second type of curve which is distinguished by symmetrical spread of response to both higher and lower frequencies Katsuki noted synchrony between impulse discharge and sound wave only below circa 800 cps and said "Therefore the volley theory of hearing is certainly not valid for pitch discrimination of high frequency sounds." He and his associates report that the neurons with characteristic frequencies below 400 cps exhibited symmetrical tuning curves, while only curves with sharp high frequency cut-off appeared if the unit's characteristic frequency was high. Both types of curve were found for fibers tuned to frequencies between 400 and 3000 cps.

Kiang and his associates (1962, 1965) have given us the most extensive data on responses of individual units in the auditory nerve His group has worked with the cat. They found all "primary" elements which were prob-

ably first order neurons to have characteristic frequencies and tuning curves of the type Tasaki described They have not found the symmetrical curves Katsuki reported as a second type Individual fibers are arranged tonotopically within the auditory nerve Fibers with characteristic frequencies below about 5000 cps each exhibit a series of preferred firing times, with the interval between successive firing times being the reciprocal of the characteristic frequency Kiang (1965) attributes this phenomenon to mechanical properties of the cochlea and to the properties responsible for triggering the nerve unit He feels that substantial information including information regarding intensity is time locked One phenomenon of interest which he and his associates observed was that fibers with characteristic frequencies up to 2000 cps could be time locked to clicks at rates up to 100–200 per second In this connection Kiang remarks, It would seem that *the stimulus rate can have more than a single correlate at the neural level The many different response characteristics that change with stimulus rate may each be functionally significant for any number of specific behavioral discriminators*" Elsewhere he adds, with a reference to Licklider (1951) It would appear that the psychophysical dimension of pitch, which has been frequently thought to be unitary has at least two correlates at the auditory nerve level"

Kiang (1965) reports the characteristic frequencies of 374 single fibers An astonishing relationship emerges if one tabulates these characteristic frequencies as is done in Table 3 Only eight fibers, that is only about 2 per cent of the total had characteristic frequencies in the octaves below the one centering at 500 cps Assuming reasonable parallelism in audibility range between the cat and the human below 10000 cps, Table 3 may be interpreted as indicating that almost no elements were encountered with characteristic

TABLE 3 *Tabulation by conventional audiometric octaves of the characteristic frequencies (CF) of the 374 single fibers of the cat s auditory nerve reported in Appendix A by Kiang (1965)*

Center Frequency of Octav Band	Number of Fibers with CF in Band
31	0
62	0
125	
250	6
500	39
1,000	45
2,000	81
4,000	49
8,000	102
16 000	42
None reported	8
Total	374

frequencies in the lower four octaves of the cat's auditory range whereas the proportion increased rapidly in the transition from 500 to 2000 cps, and thereafter the proportion remained high. *It is intriguing to plot this* distribution as is done in Figure 3 so that one achieves a rough visual analogue to the audiogram of kernicteric hearing loss shown in Figure 1. This comparison *highlights the fact that kernicteric hearing loss is less* in the frequency range where the characteristic frequencies of individual VIIIth nerve units are rare than in the range where characteristic frequencies are more *common*. *Each figure shows two plateaus, one ending at* 2.0 cps and the other starting at 2000 cps, with a fairly smooth interweaving transition. One must not assume that such a parallelism implies a full *analogy but it seems reasonable to conclude that* any central lesion which might disturb discrimination for peripheral tonotopic analysis without disrupting discrimination for time locking to a comparable degree would have *a much more* severe effect on response to high frequencies than to low ones.

Another way of viewing the matter is to note that Kiang (1965) found one element with a characteristic frequency of 110 cps another of 130 cps, and third at 250 cps and a fourth at 290 cps. Thus only four units were encountered that were tuned to frequencies in the lowest three and a half octaves or so of the auditory range. By contrast, there were twelve units with characteristic frequencies between 320 and 400 cps. Thereabove the incidence was substantial and fairly uniform. It thus appears that one may take 300 cps as the approximate lower boundary of the range wherein elements with specific frequency tuning are found in copious number. A substantial span of the lowest audible frequencies, a span which according to the place theory is served by about 20 per cent of the organ of Corti seems to be very sparcely supplied with specifically tuned units within the auditory nerve. It thus appears reasonable to conclude from the data Kiang has reported that tonotopic representation is poorly preserved for low frequencies and that the place mechanism is not the primary one operating in their perception. It is likely that a time-locked (volley) mechanism which does not require that individual units be sharply tuned to the stimulus frequency *operates here instead. Remember that it is toward the low fre*quencies that the responsiveness of all primary neural units spread as stimulus intensity is increased.

The behaviors of single units within the cochlear nuclei have much in common with units in the auditory nerve but some important differences also exist. For example Galambos and Davis (1943) in their well known pioneer study obtained characteristic curves somewhat akin to those that have since been demonstrated for primary units of the auditory nerve.

Rose (1960) reports on a substantial array of data obtained during his study on tonotopic organization in the cochlear nuclei of the cat. His paper purports "to prove that there exists an orderly tonotopical arrangement of single neurons in all segments of the cochlear complex." He adds that,

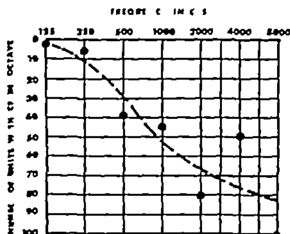


FIG. 3. Distribution by audiometric octaves of the characteristic frequencies of single units in the auditory nerve of the cat which, among the 374 units on which Kiang (1965) reported in detail, had characteristic frequencies within the conventional audiometric range

" If one divides the cochlear complex on cytoarchitectural grounds into three major subdivisions all the experimental data support the presumption that each of these three divisions commands a full tonal spectrum." The three distinct areas are the dorsal cochlear nucleus, the posteroventral nucleus and the anteroventral nucleus. Rose found that a microelectrode advancing within each of these areas encountered individual units whose characteristic frequencies constitute an orderly progression The transition from one major area to another as revealed by abrupt change in the best frequencies of elements, is sharp Rose says "It is actually fairly simple to account for the orderly sequences of best frequencies If an orderly arrangement of cochlear fibers and an orderly distribution of their terminals is assumed to exist" However Rose voices the view that the several areas within the cochlear nuclei do not have identical functions when he says, " it is useful to consider that functional significance of the morphological divisions in the cochlear complex may be primarily not in the different behavior of single units but rather in the way in which the neurons are organized in each division "

Rose made 630 determinations in 32 penetrations during 27 experiments. Practically all of the neural units he encountered had best frequencies in the middle and high ranges. For example, one notes that in seven of the illustrations he presents in his paper not a single best frequency is below 3000 cps. His two other illustrations show the same concentration of tuning to higher frequencies except for three units tuned to 700 680 and 140 cps respectively Rose (1960) concludes from his data, "The experiments imply that the overwhelming bulk of tissue in each division (of the cochlear nuclei) is devoted to frequencies not lower than about 2 0 kc and not higher

than 30 0 kc which suggests that behaviorally the cat should be expected to be at his best within this range"

Two facts point up the paradox inherent in Rose s interpretation of his data and in his view that frequency representation in the cochlear nuclei is strictly tonotopic. In the first place there is ample evidence that the cat has sensitivity for low frequencies that is very akin to that of human beings, at least down to about 100 cps Rose s data indicate that there is very limited tonotopic representation within the cochlear nuclei for the lowest three octaves or so of the cat s known range of auditory sensitivity A deficit of this magnitude makes it unreasonable to presume that low frequencies are represented within the cochlear nuclei primarily as replica tions of place patterns generated on the cochlear partition.

Secondly the auditory nerve may be richer in units with low characteristic frequencies than are the cochlear nuclei. About 30 per cent of the 374 auditory nerve units that Kiang (1965) studied in depth had characteristic frequencies below 2000 cps, whereas in Rose s illustrations the fraction is substantially less than 5 per cent If subsequent experimentation confirms a relation of this general type we will be forced to the conclusion that, insofar as the responses of individual units are concerned, some of the tonotopic information carried by the auditory nerve is not preserved in comparable tonotopic proportion within the cochlear nuclei Moreover the frequency range in which this decrease seems to occur is the frequency range wherein time-locking of neural discharge is still fairly definitive, while the range wherein tonotopic mapping remains predominant in the cochlear nuclei covers the high frequencies where the place mechanism according to the volley-place theory assumes full ascendancy

The foregoing observations support the opinion that the entire frequency range is not preserved well within the cochlear nuclei through tonotopic mapping. A second mechanism probably operating exclusively for very low frequencies and predominately for intermediately low frequencies seems to be required by the electrophysiological data Rose has reported This second mechanism probably is responsive to temporal features in the nerve impulse train. Rose s findings are not counter to this view since extensive neurolog ical processing of time locked sequence could have been occurring during his experiments which his search for tonotopic relations would not have revealed

In this connection, the work of Kiang *et al* (1965) on responses of indi vidual units within the cochlear nuclei is pertinent. These workers con firmed in general Rose s mapping of the cochlear nuclei into structurally different areas each exhibiting tonotopic mapping of characteristic fre-quencies in an orderly manner One may gain some idea of the distribution of characteristic frequencies these authors encountered from the illustra tions they publish Only four of the forty-five measurements depicted in these illustrations showed characteristic frequencies below 1000 cps and the lowest was 275 cps Units with high characteristic frequencies were

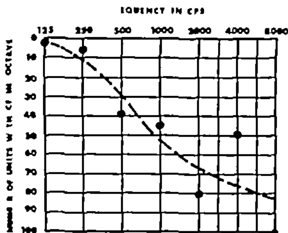


FIG. 3 Distributi by adi met le octaves of the characteristic frequencies f single it In the ditory erv f the cat which am g th 374 unit which Kiang (1965) *reported l det il, had characteristic frequencies within th con enti l diametric rang*

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Rose made 550 determinations in 32 penetrations during 27 experiments. Practically all of the neural units he encountered had best frequencies in the middle and high ranges For example one notes that in seven of the illustrations he presents in his paper not a single best frequency is below 3000 cps His two other illustrations show the same concentration of tuning to higher frequencies except for three units tuned to 700 680 and 140 cps, respectively Rose (1060) concludes from his data "The experiments imply that the overwhelming bulk of tissue in each division (of the cochlear nuclei) is devoted to frequencies not lower than about 2 0 kc and not higher

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describes best how high frequencies are processed by the central nervous system. This view is a rephrasing of the volley-place theory based on electrophysiological findings. Moreover, the previous discussion of single neuron response would seem to indicate that an almost purely time-locked analysis occurs for frequencies below about 300 cps and that time locking retains substantial albeit progressively decreasing importance from 300 cps up to 2000 cps or above. Conversely, electrophysiological findings imply that the place mechanism begins to operate at about 300 cps, that its efficiency increases progressively above this point and that it becomes the sole basis for frequency discrimination from 2000–3000 cps upward.

SUMMARY

The present paper reviews several lines of reasoning which underlie the hypothesis that when kernicterus produces a loss in threshold sensitivity it does so by virture of lesions within the cochlear nuclei and that these lesions disrupt analysis of tonotopic (place) information more radically than they do analysis of time-locked (volley) information. The following are presented as arrays of data supporting this hypothesis.

1. Kernicterus has been found to produce lesions in the cochlear nuclei. These are characterized, as are kernicteric lesions elsewhere in the central nervous system, by generalized depopulation of neurons. There is not definitive evidence that any inner ear damage results from this malady.

2. The audiometric configuration characterizing kernicteric hearing loss clearly shows a frequency dependent impairment. Most typically there is a plateau of mild loss (circa 30 dB ISO) from 250 cps downward, a plateau of substantial loss *(circa 75 dB ISO) from 2000 cps upward and a fairly smooth transition between* these plateaus. Usually, however, the increase in loss is most abrupt in the 250–1000 cps range and averages about 23.5 dB of shift in the octave showing the greatest change.

3. Several kinds of experiment have demonstrated that listeners can achieve frequency discrimination and pitch experience from periodic, low frequency fluctuations of sound under circumstances where excitation is either restricted to regions of the cochlea serving higher frequencies or where excitation is uniformly distributed within the cochlea. Such periodicity pitch experiences are most prominent when stimuli fluctuate less that 300 times per second and they grade off to non-existence by about 2000 cps. Most students of periodicity pitch phenomena interpret them as evidence of the operation of a volley-sensitive mechanism most probably in the cochlear nuclei.

4. Electrophysiological studies of responses of individual units within the auditory nerve show that each element has a characteristic frequency to which it is most responsive. *These elements are arranged tonotopically within the nerve.* This fact, considered in conjunction with their pattern of innervation of the organ of Corti, support the place theory and the concept of the peripheral analysis of sound. However, this tonotopic representation is richest for frequencies above 1000 cps and is very sparce for frequencies below 300 cps—a fact which argues against analysis on the basis of place for low frequencies. Concurrently, moreover, individual neurons show time-locking in their responses provided their characteristic frequencies are not above several thousand cps. This time-locking, which can give rise to forms of volleying, supplies information that the nervous system probably uses for analysis on a non-tonotopic basis. Said differently, time-locked information would seem to be the primary type available for frequencies below 300 cps, place information would seem to be the primary type available above 5000 cps or somewhat lower, but both types would seem to be

generated in the intervening range Thus, a central mechanism for volley analysis appears to be required for low frequencies and pure reliance on the place mechanism can not be assumed to occur until stimulus frequencies become high.

5 Responses of individual neurons within the cochlear nucleus are of more types than in the auditory nerve indicating that this region is an analyzing and not merely a relaying center Tonotopic arrays are clearly demonstrated within the cochlear nuclei indicating that place analysis occurs but these arrays are as deficient in low frequencies as is the tonotopic representation within the auditory nerve This fact appears to be evidence that a mechanism for analyzing time locked impulse trains, or volleys, must also exist in the cochlear nuclei. The frequency span over which this volley-sensitive mechanism would be judged to operate on the basis of the characteristic frequencies encountered within the cochlear nuclei is the same as postulated on the basis of data on behavior of single elements in the auditory nerve

In conclusion, the data on period city pitch and single unit response suggest that only a volley-sensitive or time-locked mechanism operates below 2∞0–300 cps and that only a place-sensitive mechanism operates above 2500–5000 cps, with overlapping and graded utilization of these two mechanisms in the intervening range The hearing loss typifying kernicterus, when viewed in light of the foregoing, appears to embody a more severe and more variable disruption of the place-sensitive system than of the volley-sensitive one Differential damage to one of these systems as opposed to the other i not to be expected from lesions peripheral to the cochlear nuclei but probably could result from appropriate lesions in these nuclei wh re post-mortem evidenc indicates kernicteric lesions can occur These several considerations support the opinion that kernicteric hearing loss is the man festation of damage within the cochlear nucl i and that th most radical effect of this damage is to disrupt the tonotopic relaying functions, that is, place-sensitivity

ZUSAMMENFASSUNG

In dieser Arbeit wird die Hypothese diskutiert ob die Hörverluste welche manchmal nach einem Kernikterus auftreten 1) von Verletzungen innerhalb des Nucleus cochlearis verursacht werden und 2) ob diese Verletzungen die Transmission der tonotopischen (Platz) Information wesentlich mehr unterbrechen, als es eine Analyse nach dem Salvenprinzip tut Dieser Aufsatz behandelt zuerst die Art der kernikterischen Verletzungen Danach beschreibt er das Audiogramm, welches für den durch den Kernikterus entstandenen Hörverlust ein Kennzeichen ist. Die typische Kontur ist ein Plateau von leichtem Hörverlust (ca 30 dB ISO) von 250 Hz hinab ein zweites Plateau von wesentlichem Hörverlust (ca 75 dB ISO) von 2000 Hz aufwärts und ein gradweiser Übergang zwischen diesen beiden Zunächst wird in dieser Arbeit der psycho-akustische Beweis diskutiert dass es jedoch ein Mechanismus des Salvenprinzipes gibt wie es die Experimente der Periodizitätstheorie zeigen Die Erfahrungen zeigen dass die Periodizitätseigenschaften des Ohres meist ausgesprochen sind wenn die Stimuli weniger als 300 Hz fluktuieren und bei 2000 Hz ganz verschwunden sind Zuletzt behandelt diese Arbeit die elektro-physiologischen Studien über die Reaktion der einzelnen Neuronen innerhalb der Gehörnerven und Nucleus cochlearis. Diese Studien zeigen, dass die neuralen Elemente in tonotopische Ordnungen arrangiert sind. Die Verteilung der charakteristischen Frequenzen bei diesen Versuchen zeigt dass diese tonotopische Darstellung bei Frequenzen über 1000 Hz am reichsten und bei Frequenzen unter 300 Hz am geringsten ist Also eine Tatsache die gegen die Analyse auf Grund von Platz für Niedrigfrequenzen streitet In gleicher Weise zeigen aber die Neuronen mit ihren entsprechenden niedrigeren charakteristischen Frequenzen dass ihren Reaktionen das Salvenprinzip zugrunde liegt. Dieses Salvenprinzip scheint in erster Hand der vorhandene Typ für Frequenzen unter 300 Hz zu sein. Bei Hochfrequenzen scheint die Platzinformation der vorhandene Typ zu sein, aber beide Typen scheinen im dazwischenliegenden Bereich erzeugt zu sein Alle diese Ansichten unterstützen die Auffassung, dass der nach dem Kernikterus erhaltene Hörverlust von Schädigungen des Nucleus cochlearis verursacht ist. Der wesentlichste Effekt dieser Schädigung ist, dass der platzempfindliche Mechanismus unterbrochen wird während der Salven (Volley) Mechanismus verhältnismässig unverändert bleibt.

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ACOUSTIC TRAUMA IN REGULAR ARMY PERSONNEL

Clinical Audiologic Study

BY

ALTTI SALMIVALLI

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FROM THE OTOLARYNGOLOGICAL UNIVERSITY CLINIC, TURKU FINLAND
(HEAD PROF OTTO H MEURMAN M.D.)

ACOUSTIC TRAUMA IN REGULAR ARMY PERSONNEL

CLINICAL AUDIOLOGIC STUDY

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CONTENTS

I. INTRODUCTION

OBJECTS OF THE INVESTIGATION

In the present-day developing society hearing losses due to loud noise are constantly claiming more attention. Advances in industry the use of ever greater physical and chemical forces have contributed to increase the number of these lesions. Another factor is the development of national defence, the introduction of new powerful weapons and more efficient gunnery training. By reason of their frequency these acoustic injuries have become a current medical and technical problem of ever-increasing social significance.

In practice the noise caused by all firearms and to a great extent industrial noise also has a sound pressure exceeding the level of damage risk to hearing. Not only the intensity of a noise but its other characteristics above all its duration play a part in the origin of acoustic trauma. Looked at from the physical standpoint continuous steady-state noise and intermittent noise can each be differentiated from the sharp loud noise produced by reports and blasts. In accordance with the etiological factors in each case the correspond ing auditory injuries should be put in their own special groups. In actual fact there are entirely different physical time and intensity factors involved in each case.

Injuries to hearing can be investigated by two widely different means objectively and psychoacoustically The former method is used chiefly in test animals the latter in studying human material to determine the clinical pattern of hearing loss. In recent investigations it has been possible to approximate the objective and the psychoacoustic methods more closely On the basis of known clinical patterns attempts are made to form orientating conclusions about the locus and development of acoustic lesions

The importance of audiologic tests in the diagnosis of auditory lesions cannot be disputed. The clinical value of the various tests however differs. There is no one test that could alone supersede all others. On the other hand there are a great number of tests whose clinical value has been challenged. In general, the significance of single audiologic tests has been overestimated their anatomic counterparts in the cochlear or retrocochlear hearing process have often been thought to be associated very exactly with pathology of a given circumscribed cell group With good reason one can speak of over diagnosis in many cases. An audiologic analysis of a hearing loss presupposes an overall picture based on many different tests. A hearing loss must be studied in all its various aspects in an attempt to form an opinion of the functional circumstances in the ear i.e. of the clinical pattern of the damage incurred Reliable information on the value of a certain hearing test

can only be obtained by comparing the audiometric results with pathologic anatomical findings. However to eliminate the effects of autolytic processes an analysis of morphological changes in the inner ear does almost invariably necessitate vital fixation and this is not possible in practice. Therefore when comparing the clinical and the pathologic anatomical findings the statistical probability of great masses will have to suffice For this purpose testing of large groups with well known etiological factors and morphological changes is *required*

Although hearing losses caused by loud noise have been the subject of research for almost a hundred years their clinical pattern must still be considered incompletely known and this applies above all to detonation injuries In general the material analysed has been small and lacking in uniformity The methods used have differed greatly and so has their reliability Hearing losses due to completely different causes e.g to continuous noise and to sudden sharp detonations and explosions have been compared

In the present investigation an attempt is made to chart the clinical pattern of acoustic trauma due to detonations by means of audiologic tests recommended (Davis 1962) for a clear functional and diagnostic strategy The methods were chosen so as to permit the use of all types of clinical audiometer available without any expensive additional apparatus. Special attention and interest was devoted to the following points

1) The occurrence development and prognosis of acoustic trauma
2) Audiologic analysis of acoustic trauma and the possible diagnostic value of such analysis.
3) Possible anatomic localization of acoustic trauma by means of audiologic tests
4) Disability due to acoustic trauma.
5) The physical characteristics of gun noise from the etiological point of view

II REVIEW OF THE LITERATURE

A. ACOUSTIC TRAUMA

The concept acoustic trauma (AT) has been variously interpreted in the course of time According to Ruedi and Furrer (1947) while after the first world war AT denoted damage to the ear due to sound waves (Schallwellen) explosive and detonation injuries were due to a physically vaguely defined blast impulse — "Explosionsstoss Ruedi and Furrer themselves took the concept AT more widely as including auditory lesions due not only to noise but to firing, blast and blunt skull injuries. Lehnhardt (1965) concurs in the classification presented by Ruedi and Furrer Some textbooks (e.g. Scott Brown, Ballantyne and Groves Diseases of the Ear Nose and Throat 1965) also interpret AT as including all auditory changes caused by loud noise The above authors state as follows "The effect of repeated short or relatively small explosions is the same as that induced by noise and is considered as noise induced deafness and add that it is confusing to accept the terminology of chronic explosive trauma or of detonation trauma. Glorig (1958) says in his discussion. Acoustic trauma is an ambiguous term and may mean either trauma caused by sound or 'trauma to the ear and continues "Most of the descriptive names for hearing loss tend to identify the agent that caused the loss for example noise-induced hearing loss occupational hearing loss barotrauma, etc. "Acoustic trauma is an exception to this usage in that it is used to denote two different things one, the cause of the loss and two the location of the damage. To eliminate the confusion that arises from the use of ambiguous terms we suggest an agent-identifying scheme for classifying industrial hearing losses. In this scheme "acoustic trauma means *only* "hearing loss caused by acoustic stimuli Auditory trauma is suggested as the more precise term to denote general trauma to the organ of hearing. The meaning of auditory is limited to the ear or to hearing whereas acoustic although it refers to the ear or to hearing, also denotes sound or the science of sound. A proposed classification of occupational hearing loss (Glorig 1958) is presented in Table 1 There are many reasons why it is difficult to differentiate etiologically a limited group of AT due only to "sudden explosive blast from other auditory lesions due to loud noise. Such causes are for example firing of automatic weapons multiple firing (by several people) and especially group firing from a shooting gallery in which case the duration of a report may be extended over a long time and the produced sound pressure burst resembles intermittent noise. Ward Fleer and Glorig (1961) consider that hearing losses due to firing can be distinguished neither clinically audiologically nor histologically from those due to noise. According to Davis (1957) there are three forms of hearing loss that are induced by

Table 1

Occupational hearing loss

Cause of hearing loss	Medical name	Legal name	Suggested names: Agent identifying	Damage identifying
continuous noise exposure	noise-induced hearing loss or occupational hearing loss or frequently acoustic trauma	occupational hearing loss	noise-induced hearing loss	auditory trauma (caused by long continued noise-exposure)
sudden explosive blasts	acoustic trauma	acoustic trauma	acoustic trauma (to the ear)	auditory trauma (caused by sudden noise)
mechanical blows to the head and/or ear	acoustic trauma	acoustic trauma	mechanical trauma (to the ear)	auditory trauma (caused by blows to head)

From Glorig, A., 1958 Noise and Your Ear

noise 1) temporary threshold shift 2) permanent hearing loss that is produced in man by repeated exposure to loud sounds over months or years and is also called occupational hearing loss and 3) permanent hearing loss produced by very brief exposure to very loud noise It has been proposed that the term acoustic trauma" be reserved for this third type.

B HISTORICAL CONSIDERATION OF ACOUSTIC TRAUMA

The history of acoustic trauma from shooting and explosions goes back to the invention of gunpowder The Chinese are assumed to have known gunpowder as early as in the first century A.D In Europe gunpowder has probably been used before 1325 An Oxford manuscript De Officis Regnum dating from that year contains an illustration of a gun There is also authentic information on cannon and gunpowder recorded in England in 1334 in France 1338 and in Florence in 1326 (Korkis 1952) The earliest preserved record of AT due to *cannonading is from the year 1591 (Alberti quoted by Goldstein 1933) An* 1866 issue of the "Lancet includes advice to use cotton to avoid injuries to hearing from firing This indicates that as early as a hundred years ago AT presented a medical problem.

A great number of researches on AT have appeared since. The most important studies from the tuning fork period are probably those of Bezold and Siebenmann (1908) and Uffenorde (1922) The first few extensive papers based on audiometry were published by Shambaugh 1935 Bunch 1937 and *Larsen 1939 The newer literature in this field is considered to begin with*

the publication of Ruedl and Furrer's "Das akustische Trauma" in 1947. A good review of the literature with references is included in Kryter's monograph of 1950 and Lehnhardt (1965) has prepared a detailed summary of more recent results.

C. GENERAL FEATURES OF ACOUSTIC TRAUMA

1) NOISE

Noise is any unwanted sound (Glorig 1958). As a concept, noise is an irregular subjective sound perception and sensitivity to noise varies widely from one individual to another, depending upon the momentary psychic and physical condition of the individual. Noise is a sound without agreeable or musical qualities but including certain subjectively undesirable sensations (Larsen 1939). The characteristics of noise are: 1) intensity, 2) frequency combination or noise spectrum, 3) duration, and 4) loudness in the situation concerned (Larsen 1939). On the basis of its physical qualities and clinical effects, noise can be classified qualitatively as 1) continuous noise, 2) intermittent noise, 3) detonation, and 4) explosive blast.

The damage risk level of noise should be so defined that 95—98 per cent of those exposed on the job to critical levels do not sustain acoustic trauma (Slawin 1957). In the case of extended exposure, the critical noise level has been reported as ranging from 80 to 1?0 dB (Bunch 1937, Peyser 1940, Growe 1947, Siirala 1952, Kryter 1952, Sataloff 1953, Meyer zum Gottesberge 1954, von Schulthess 1957, etc.). There are very few data available concerning the maximum intensity of reports or blast below which no damage to hearing presumably occurs. This scarcity of information undoubtedly stems from several causes. In part, such data may be considered military secrets. As regards noise intensity and noise spectrum, weapons of various types differ to a very great extent. Most soldiers do much shooting with different types of gun. It must be taken into account in addition that a smooth concrete wall will reflect 96 per cent of the acoustic energy striking it (Perlman 1941). This being so, it matters greatly whether the firing takes place alone or in a group, whether in an open field or in a shooting gallery. According to Pfander (1965) the permissible maximum level (without ear protection) is 165 dB ≤ during ≤ 0.003 sec. per day, corresponding to 155 dB/0.03 sec. and 145 dB/0.3 sec. (Fig. 1).

Noise in which energy is concentrated chiefly on the 1 000—4 000 cps range is the most traumatising to the ear from the hydrodynamic point of view (von Békésy 1960). In principle, very high intensity noises are more distinctly associated with the higher frequencies than are less intense noises (Lehnhardt 1965). The physical maximum of industrial noise ranges from 2 000 to 4 000 cps (Larsen 1953). Kylin (1960) studied the noise in 2,380 factories. In the case of most of the noises exceeding 80 dB the maximum

tating and acute cases During training practices large amounts of explosive are detonated in the close proximity of conscripts. Flodgren (1943) found that among 88 injured during such a practice there were 48 ruptures of the eardrum 10 cases of bleeding of the eardrum and 43 detonation injuries of inner ear type. In Finland Björk (1959 1961) studied the clinical pattern of AT due to acute detonation or explosion trauma. Relatively slight firing produces permanent hearing loss in 10—15 per cent of servicemen (Olaison 1958 1962 Lahikainen and Salmivalli 1963) Anti-aircraft personnel using ear defenders escaped acoustic injuries whereas in a control group without ear protection (only cotton wool) AT developed in 18 per cent (Schneider 1950) What arouses special interest in the various studies is the high incidence of acoustic injuries. Obviously Larsen s (1953) general rule applies i.e. that all those exposed will have AT if the exposure to a sufficiently loud noise lasts long enough.

3) RATE OF DEVELOPMENT OF AT

The speed at which AT develops depends essentially on the degree of stimulation its duration and regular repetition and on the other hand on individual characteristics (Schubert 1944) Some acoustic injuries are permanent some are temporary On this account the subject studied should be allowed a sufficiently long rest period generally estimated at 24—48 hours for the result to be reliable.

In some cases a single gun report or a few days exposure to noise on the job is enough to produce a permanent hearing loss. Others however can work under the same conditions for years and still retain normal hearing. It is generally agreed that noise injury develops at first rapidly later more slowly and may come to a standstill at a given stage which depends mainly on the noise level. Glorig Ward and Nixon (1961) have stated that the damage reaches this maximum in 10—12 years regardless of the exposure. Kylin (1960) also studied workers exposed to continuous noise. He found that when loudness exceeds the damage risk criterion even three months suffice for AT to develop The major part of the injury develops during the first five to ten years after which continuous exposure to noise affects hearing to a less extent than does age.

Less is known about the rate at which acoustic injuries develop as a result of firing. In gunners, according to Reid (1948) it is during the first one to two years that the trauma mainly develops Many are deafened by a few gun reports others only show slight changes after years of service Collins (1948) study is based on 108 men complaining of injury to their ears to the War Office. In 22 of these AT developed in connection with the first round of shooting. Of 100 gunnery instructors shooting for 7½ hours daily only 5 had normal hearing after a period of eight and a half months (Stewart *et al.* 1946) After ten to twelve months of service the impairment in hearing seems

to become stabilized and further loss thereafter occurs slowly if at all. Reid (1946) made experiments with blank charges in the laboratory He tested the hearing of all subjects after a single shot or round of shooting. After five or six rounds had been fired there was little or no further change in the peak loss which remained at about 60 dB The hearing loss was temporary' all subjects showed less hearing loss on subsequent exposure a few months later The difference could be as much as 20—40 decibels. This decrease in sensitivity affected mainly the lower frequencies of those involved (usually 1 000—2 000 cps) but higher frequencies also became resistant

f) RECOVERY

In the great majority of cases AT has a tendency to recover spontaneously If recovery does not start within two months the injury evidently is permanent (Hagermann 1942a) In the ordinary course of events, restitution takes place within two to seven months at least in acute cases in a chronic case the changes obviously are more permanent (Hagermann 1942b) Six months after the end of firing, significant recovery no longer occurs and the loss of hearing can be considered permanent (Stewart *et al.* 1946)

Recovery after a temporary hearing loss is generally completed in a period of ten days. Clinical recovery however does not presuppose that the organ of Corti is restored to normal (Reid 1948) In recent years Beagley (1965a) has shown by electro-physiological means that the recovery of sensitivity is clearly greater than the recovery of the capacity to generate CM voltages. Altenburger (1963) studied acute detonation injuries and found that symmetrical and asymmetrical injuries take about the same time to recover and the definitive loss of hearing can be recorded after six to ten weeks Slight and severe lesions do not differ with respect to duration of recovery In Ogden's (1950) opinion the period of recovery is shorter still. Whatever recovery there is, takes place in 24—48 hours Ruedi (1957) however has described late recovery after five to seven years.

Russi (1946) on the basis of cases studied, defined recovery from AT as follows 1) C_5 is restored in all cases most completely in those least exposed to noise on the job 2) Recovery occurs in the entire hearing range. 3) Even in severe hearing losses hearing for whispered voice can be restored but usually only to a very limited extent. 4) The threshold improvement reached during a short week-end rest period (c. 60 hours) returns to the previous level in the course of one working day According to Davis *et al.* (1950/1943) recovery from AT follows an exponential curve being rapid at first but later retarding. Von Schulthess (1957) is in agreement with this view It is probable that a permanent dip develops after incomplete and asymmetrical recovery from a temporary acoustic injury (Gravendeel and Plomp 1959 1961 Kylin 1960) The point in time after which there is no longer auditory fatique i.e. no longer any temporary hearing loss with sub-

sequent recovery coincides with the point beyond which no progression of damage occurs (Theilgaard 1951) This is obviously due to the fact that those elements of the inner ear which fatique when exposed to experimental or occupational noise are possibly identical with those destroyed during years of exposure to noise.

D OBJECTIVE LABORATORY FINDINGS

MORPHOLOGICAL AND PHYSIOLOGICAL CHANGES ASSOCIATED WITH ACOUSTIC TRAUMA

Because the inner ear undergoes autolysis rapidly it is only by means of vital fixation and accordingly only in experimental animals that the pathologic anatomical changes can be satisfactorily demonstrated. In animal tests however it is not possible to compare morphological changes with audiologic results Preyer's ear reflex has often been used as a rough orientating test for evaluating hearing loss Since in AT loudness recruitment is frequently present, the Preyer test may convey an entirely false idea of the auditory status The pathologic anatomical changes associated with AT in the human ear have been studied by e.g. Growe Guild and Polvogt 1934 Wolff 1942 Ruedi 1957 Habermann 1960 and Ikarashi, Schuknecht and Myers 1964 A very great number of studies on pathologic anatomical changes in noise injuries of experimental animals have appeared since the days of Wittmaack (1911) These studies have the common feature of showing great individual differences in severity and time of onset of the hearing losses.

The outer hair cells with their supporting elements are first damaged and destroyed. Gradually at the centre of the damage the inner hair cells and the entire organ of Corti undergo destruction (Ruedi and Furrer 1947 Guild 1952 Davis *et al.* 1953 etc.) Beagley (1965a) states as follows "A radial gradient of external hair cells was also observed. The external hair cells in the innermost row were damaged most the middle row next and the external row least The pillar cells were bent or collapsed in those ears with little recovery resulting presumably from greater initial injury The Hensen—Deiter's junction was intact in the severely damaged ears but a large cleft was seen in those ears with little injury and much recovery There is a direct relation between threshold shift and hair cell injury and an inverse relation between threshold shift and splitting. There is by inference an inverse relation between hair cell damage and splitting

Degeneration of ganglion cells and nerve fibres may have occurred secondarily after the destruction of hair cells (Ruedi and Furrer 1947 Guild 1952) Beagley (1965a) also failed to note any changes in nerve fibres or nerve endings fourteen days after the trauma. On the other hand even assuming that the majority of nerve fibres and ganglion cells are destroyed,

the pure tone threshold remains normal (Dandy 1934 Schuknecht and Woellner 1953 Neff 1947 Wever and Neff 1947)

The greater sensitivity of the outer hair cells to a traumatizing sound is assumed to be due to anatomical and mechanical not to neurophysiological causes. The external hair cells are located at the centre of the basilar membrane whereas — thanks to the dense connective tissue of the limbus — the inner hair cells are relatively well protected against the fluid movements produced by sound energy Thus owing to purely mechanical factors the stimulating waves of the internal hair cells must be stronger (Davis *et al.* 1953 Meyer zum Gottesberge 1954) It follows that the movement and disruption of the external hair cells are greater especially when we take into account the observation by Békésy (1941 1948) that in man the basilar membrane is in practice a flaccid membrane which can be likened to a gelatinous sheet covered by a thin layer of fibres.

An extremely severe trauma, usually due to explosive blast may result in rupture and total destruction of the organ of Corti and a rupture of basilar membrane (Ruedi 1957 Covell 1953) At autopsies made during the war petechial hemorrhages in the internal ear were common findings (MacFarlan 1941) It is possible that also in cases which did not terminate fatally bleeding occurred in the inner ear and the resulting fibrosis might account in part for the permanent character of the inner ear deafness (Korkis 1952)

Among those who have studied the ultrastructural changes associated with AT Spoendlin (1958 1962) Engström and Ades (1960) Kolde *et al.* (1960) and Beagley (1965b) deserve special mention Changes were found in the hair cells the supporting cells as well in the nerve endings and ganglion cells. In the basilar membrane too irregular connective tissue fibres scar formations were demonstrated. The first morphologic changes to occur were a great increase in the number of dark inclusions within the apices of the outer hair cells. These inclusions probably are products of the oxidative metabolism possibly intensified metabolism No significant morphologic changes have been observed immediately after intense acoustic stimulation within a period of a temporary threshold shift (TTS) Thus TTS does not appear to be related to demonstrable ultrastructural alterations in the hair cells. On the other hand, prolonged stimulation results in visible morphologic changes within the hair cells and nerve endings even though there is no permanent hearing loss at rest This may be due to increased metabolic activity The nuclei of the hair cells show alterations which are a sign of increased activity Nuclear size increases the chromatin net work becomes irregular nucleoli are very clearly discernible. Later the mitochondria (which contain oxydation enzymes and produce unspecific energy for the specific function of the hair cells in other words play a part in changing mechanical sound energy into nerve impulses) lose their characteristic lamellar or membraneous structure begin to swell and degenerate simultaneously with distinct nuclear changes. Similar changes occur at the same time in the supporting cells and possibly in the ganglion

cells. The morphologic alterations seem to point most probably to oxygen lack in the inner ear during exposure to noise.

At the early stage of AT the most pronounced biochemical change in the internal ear is the disturbance of the energy producing system which may arise through oxygen deprivation or mechanical disruption of the respiratory chain in the mitochondria. Koide and his co-workers (1960) noted that oxygen tension was reduced by exposure to loud sound stimulation (105 phons) The decrease in oxygen tension in the inner ear was more severe than the decrease of oxygen caused by breathing the 5 per cent mixture. Shock waves (e.g. firing) failed to produce any observable change in oxygen tension. In these cases the active mechanism is mainly a vibration effect The so-called physico-chemical theory of the onset of acoustic trauma assumes that chemical reactions on the biological structures of the inner ear e.g. denaturalization of protein can be initiated by infinitesimal amounts of vibratory energy Thus it is probable that the mitochondria may be affected rather by the mechanical forces than by the oxydation during exposure to sonic energy Decrease in the oxidative phosphorylation of the outer hair cells is the first event following sonic vibration. This should be followed by a decrease in the respiration of the cells. Accordingly on the basis of biochemistry the cause of acoustic trauma is similar to that of inner ear disease due to vascular accidents since decrease in the oxidative phosphorylation plays a predominant role in the onset of both diseases

Hallen Edström and Hamberger have recently (1965) reported results of an experimental series indicating—contrary to earlier findings that no significant decrease in cellular volume dry weight RNA content or cytochrome oxidase activity can be observed in spiral ganglion cells following acoustic stimulation.

In their electro-physiological studies Davis *et al.* (1953) showed that the cochlear microphonic input-output curve from the guinea pig cochlea following acoustic trauma showed two distinct shifts First there was a shift downwards of the whole curve identified by a drop in the maximum voltage and second, a further shift to the right in addition to the apparent shift to the right due to the drop in voltage The first shift which is a drop in voltage output is undoubtedly related to loss or damage of hair cells The second shift suggests an inner ear conductive lesion in the supporting tissues of the organ of Corti which tends to isolate the hair cells from the acoustic stimulus. There was an inverse relation between the cochlear microphonic threshold shift and the extent of separation of the Hensen's cells and the Deiter's cells (Beagley 1965a) It appears that such a split in some way protects the inner ear Békésy observed (1953) that the hair cell movement is reduced to one-fourth after cutting the Hensen's cells free from the reticular lamina and the basilar membrane.

The summating potential does not reach a maximum below the limits causing anatomic injuries It increases typically in moderate anoxia and slight chemical injuries (Davis 1957 1958) Changes similar to those seen in

anoxia are also encountered in connection with acoustic stimulation. Thus it seems possible that the state of the mitochondria in the apical part of the hair cells determines the functional capacity of the cell (Koide *et al.* 1960)

Modern pathologic physiology and anatomy indicate that noise does not — as previously assumed — simply hammer on the hair cells until they break up mechanically This applies at the very most to extremely high sound pressures over 140—150 dB At all normal sound intensities the damage starts within the hair cells with disturbance of the metabolism. Expressed in other terms noise is qualitatively though at the same time quantitatively an adequate supermaximal stimulus to the auditory apparatus. For this reason the physiology of the sense organs is intimately connected with the pathology of acoustic trauma (Lehnhardt 1965)

E. PSYCHO-ACOUSTIC FINDINGS

1) PURE TONE AUDIOGRAM

There is no pure tone audiogram pathognomonic of acoustic trauma. Hagermann (1942b) distinguished three typical audiograms 1) A C_5 dip in about 40 per cent 2) an abrupt high tone hearing loss in about 20 per cent, and 3) a divided dip in about 10 per cent. The remaining 30 per cent had more irregular audiograms. Ruedi and Furrer (1947) separate only two typical audiograms. The audiologic finding produced by continuous noise detonation or a blunt skull injury is characterized by a typical C_5 dip The absence of C_5 dip is typical of injuries due to explosions or blasts which instead show an abrupt high tone loss. It is true that the study of Ruedi and Furrer also includes distinct divided dips. These authors attribute the differences in audiogram types chiefly to etiological factors. Amounts of explosive exceeding 20 gm as well as cannon with a calibre of more than 75 mm, and gun reports with over 1 000 gm gunpowder do always cause a blast injury that is hearing loss of abrupt type. However numerous "blast injuries have been found in cases of AT due merely to rifle reports (Lehnhardt 1965) On the other hand a typical explosion may result in audiograms showing not only abrupt but pancochlear injuries and particularly if the eardrum is not ruptured also typical C_5 dips (Seiferth 1953 Altenburger 1963) Reid (1946) also considered that the acoustic traumata caused by various firearms do not differ distinctly In addition all audiogram types seen in permanent AT do in fact occur at some stage of temporary AT (Reid 1948) In studying the development of AT Meyer zum Gottesberge (1954) found that there is first a dip which widens and deepens but gradually this change loses its character of dip and there occurs a high tone loss which extends towards the low frequencies and finally AT comes to resemble degenerative hearing loss. Collins (1948) collected, from the War Office, subjects complaining of traumatic

deafness — a series selected to the extent that 108 subjects included only five with a typical tonal dip His cases greatly resemble patients with Menière s disease with respect to audiometric findings and subjective symptoms.

Matzker and Becker (1967) described a special form of AT which they termed "Akustischer Unfall (acoustic accident) These are characterized by a basin or U-shaped loss in hearing which is maximal at 500—1 000 cps The etiological factor is brief exposure to loud noise with the patient in a bent forward position. The pathogenetic basis is stated to be stretching of the cervical sympathicus due to the bent-forward position with a simultaneous marked increase in intracranial blood pressure. This audiogram cannot be pathognomic of the above-described type of injury Franz (1963) found among 6,000 audiograms 14 with the above basin-shaped loss These 14 cases had a widely varying etiology The majority eight of fourteen were hereditary the rest infectious toxic or due to skull lesions The pathological change can be cochlear retrocochlear or central (Franz)

3) SPEECH AUDIOMETRY

Very few reports are available on speech audiometric results in AT In theory the intelligibility of speech is not very much affected by hearing loss at frequencies higher than 2 000 cps since most of the speech sounds have low component frequencies (T Palva 1952) On the other hand the essential speech range extends from 250 to 4 000 cps Thus there may be a slight impairment of speech discrimination in AT too The so-called "critical speech area lies between 30 and 40 dB in the range from 1 000 to 2 000 cps. If a hearing loss is in excess of this the intensity of the ordinary spoken voice no longer affords a sufficient stimulus In general however workers exposed to noise have surprisingly good hearing for speech (Glorig and Davis 1961 Lehnhardt 1965)

The elimination of high tones affects the intelligibility of consonants more than that of vowels (Fletcher 1929 Wagner 1954) The first speech sounds to be affected by distortion are *s* and *ʃ* followed by *m n* and *ŋ* which are already very difficult to discriminate when the cut-off frequency is about 2 500 cps (Wagner 1954) However in the case of consonants in particular it must be borne in mind that intelligibility often depends decisively on the sounds preceding and succeeding the sound in question (Fry 1964) In low pass filtration speech discrimination began to suffer when the cut-off frequency fell below 2 000 cps (A. Palva 1965) The first mistakes to occur were evident in the discrimination of consonants At 2 000 cps typical mistakes were the addition of a consonant in front of a word beginning with a vowel the substitution of *h* for *s* and the confusion of *m n* and *ŋ*. Only after the cut-off frequency of filtration fell below 1 500 cps did mistakes begin to occur in the discrimination of vowels (A. Palva 1965) In principle AT can be regarded as a kind of low-pass filter and so the result might be correlated.

3 THE RECRUITMENT PHENOMENON

The discovery of the recruitment phenomenon is ascribed to Fowler (1928) Following the statement by Dix, Hallpike and Hood (1948) that recruitment is pathognomonic of end-organ disease study of this phenomenon acquired true clinical importance in differential diagnosis. Recruitment is defined as a phenomenon in which subjective loudness appears to increase more rapidly than normal when the growth in loudness is related to increments in physical intensity above threshold. Or as stated by Lundborg (1952) recruitment is said to be present in an ear when the sensitivity to intensity is subnormal at low intensities but normal or relatively better at higher intensities.

It has been customary to divide the methods of measuring recruitment into direct and indirect tests Fowler introduced the alternate binaural loudness balance test (1928) It was later modified by Reger (1936) who called it the alternate unilateral equal loudness level balancing test. These two are considered direct tests But there are cases in which the hearing is depressed bilaterally and equally at all frequencies. These cannot be examined by the above direct tests. Accordingly attempts have been made to devise additional indirect tests for recruitment Unfortunately enough, most of the original studies have not been fully validated against the classical loudness balance tests and have proved disappointing in critical experiments. The most common indirect tests for measuring recruitment are IDL (intensity difference limen) FDL (frequency difference limen) automatic threshold recording with the Békésy audiometer masking or noise audiometry perstimulatory adaptation and poststimulatory fatigue. The differential diagnostic value of these tests has been challenged, even strongly because in normally hearing subjects in conductive hearing losses, and in various inner ear diseases the dispersion of measurement results is too wide while there is also overlapping of the various categories. Moreover the results are not consistent with the values for recruitment function defined by the method of Fowler or of Reger (Liden and Nilsson 1950 de Mare and Rösler 1950 Lund-Iversen 1952 Palva Goodman and Hirsh 1953 Hirsh Palva and Goodman 1954 T Palva 1956 1957a, 1958a, etc.) Nevertheless these tests can be considered valuable additional tools in determining the functional characteristics of the ear The speech-amplifying test devised by Zangenmeister (1950) which measures the threshold and pain threshold by speech audiometry is to be regarded as in a way a modification of the direct test. The gap between these two thresholds decides whether or not recruitment is present. According to Fowler too (1960) recruitment for speech is indicated when in moderately deafened ears (20—35 dB) a 5 or 10 dB increase over threshold in the loudness of speech produces a marked increase in the loudness and intelligibility of speech (a comfortable level) and more than a 20 dB increase will be too loud for comfort It is to be noted however that loudness is a psychological phenomenon, so there is after all no objective method for measuring recruitment (Harbert and Sataloff 1955)

Theories on the origin of recruitment have been advanced by e.g., Lorente de No 1933 Lurie 1940 von Békésy 1947 Dix Hallpike and Hood 1948 Meyer zum Gottesberge 1948 Tumarkin 1950 Mygind 1950 Davis 1957 and Dix 1965 In sound stimulation the vibrations of the basilar membrane increase in amplitude with the distance from the osseous spiral lamina. The outermost of the outer hair cells are thus stimulated first the inner hair cells last (dual pattern loudness theory/Tumarkin Dix) The outer hair cells operate over an intensity range which extends up to some 60—80 dB The inner hair cell system responds to the higher frequencies (dual excitation theory/Davis) In addition in pathologic processes involving a reduction in the number of the neural elements in the organ of Corti other neurons could fill the demand at higher intensities the cortex thus receiving the same number of impulses as from an ear with normal hearing.

Clinically recruitment is of great significance since investigators have tried, on its basis to separate cochlear from retrocochlear pathology (Lurie 1940 Dix Hallpike and Hood 1948 1949 Neuberger 1950 Tumarkin 1950 Eby and Williams 1951 Lundborg 1952 Harbert and Sataloff 1955 Kos 1955 Proctor *et al* 1956 T Palva 1958a, Pestalozza and Cloce 1962 Harbert and Young 1964 etc.) Pathologic anatomical findings also point in the same direction (Saxén 1938) Recruitment has however also been described in definitely retrocochlear pathology e.g. in acoustic tumours (Fowler 1950 Dix and Hood 1953 Dix 1956 T Palva 1958a, House 1964) and even in central pathology (Greiner and Pestalozza and Cloce 1962 T Palva 1961) In these cases recruitment is assumed to be caused mainly by vascular factors due to the tumour This seems to be proved by the fact that recruitment may disappear following removal of the tumour (Dix and Hood 1953) Some prognostic value also attaches to the presence of recruitment since it appears to be associated with hearing loss that is in a state of flux (Harbert and Sataloff 1955) As long as there is recruitment it is still possible for hearing either to improve or deteriorate. After the disappearance of recruitment the changes of improved hearing are slight Yet it should be added that absence or presence of recruitment does not rule out end-organ or auditory nerve damage (T Palva 1958a) Nor does the absence of recruitment according to Harbert and Sataloff exclude the possibility of the organ of Corti being injured also Indeed Davis (1962) points out that audiological tests do not make etiological or even anatomical diagnosis they test auditory function.

Thus recruitment is said to occur regularly in pathological conditions with organic changes affecting mainly the outer hair cells of the organ of Corti. Typical such conditions are traumatic hearing losses Menière s disease progressive congenital perceptive deafness and cases of acute deafness due for instance to vascular accidents Recruitment is as a rule present in AT both in temporary threshold shift (TTS) due to experimental stimulation (Davis et al. 1943 1950 Reger and Kos 1958) and in occupational hearing loss (de Bruine Altes 1946 Meyer zum Gottesberge 1954 T Palva 1957b 1958a Ward and Glorig 1961 Ward Fleer and Glorig 1961) There are however exceptions to the

occurrence of recruitment in the above studies too (Davis Palva, Meyer zum Gottesberge) Recruitment may also occur only at some particular stage of AT (Harbert and Sataloff 1955)

i) PERSTIMULATORY ADAPTION

Adaption means a decline in excitability caused by the stimulation quite apart from the existence of activity" (Larsen 1953) On the basis of Matthews (1931) electro-physiological researches Hood (1955) concluded that stimulation of the end-organ first brings about a great burst of action potential, or "on-effect lasting about 0.2 sec. This is followed by a slow decrease in the discharge frequency with time. This decrease is termed adaptation. These two nerve responses (on-effect and sustained response) demonstrated by neuro-physiological and psychoacoustic methods can be functionally impaired (Sørensen 1962)

An adaptation test was described as early as 1893 by Gradenigo A patient with an acoustic nerve tumour responded to a maximally vibrating tuning fork for a few seconds only A number of audiometric adaptation tests have been developed later Bocca and Pestalozza (1959) divided the methods of measurement as follows 1) Adaptation due to brief stimulation, 2) disappearance of tonal sensation of threshold and 3) perstimulatory adaptation of long duration. Results indicate that the various tests are not comparable (Bocca and Pestalozza 1959) T Palva (1964) divides the tests under point 3) into two subgroups 1) adaptation at threshold intensity 2) adaptation above threshold. In the latter test the contralateral ear must be used as reference point Most suitable in routine clinical work because of its greater simplicity purity and practical character is a threshold adaptation test lasting several minutes (Pestalozza and Cioce 1962 Palva 1964) Tests of short duration all differ from one another require special equipment and have the further disadvantage of not allowing time for sufficient adaptation to occur A source of error associated with the suprathreshold test is adaptation in the contralateral ear and difficulties in balancing the test tone.

Schubert (1944) suggested that the threshold adaptation should include also audiometric tests. Not until the publication of Carhart's (1957) studies, however did the threshold-tone-decay test gain greater clinical importance. In this test a continuous tone is delivered at threshold to the subject being tested. When the tone disappears the stimulus is increased 5 dB at a time until a permanent level or the end of the audiometric scale is reached.

There has been much division of opinion as to the anatomic locus of the adaptation phenomenon even in the most recent time. This fact seems attributable to the great diversity of tests used. Indeed some authors have wished to include the adaptation test among the indirect recruitment tests. Gradenigo (1893) found an excessive functional exhaustibility in affections related to the acoustic nerve. In general a pronounced pathological adaptation

has been reported especially in acoustic nerve lesions tumours or atrophy (Reger and Kos 1952 Kos 1955 Reger and Kos 1958 Pestalozza and Cloce 1962 etc.) Pathological adaptation has also been described in definitely central lesions. Kos (1955) reported on a patient with pinealoma with a normal pure tone audiogram but excessive adaptation Removal of the tumour led to normalized adaptation In multiple sclerosis hearing loss is usually slight yet adaptation may be considerable. Pestalozza and Cloce (1962) found abnormal adaptation in cases of temporal epilepsy with possible lesion of subcortical structures A tumour with consequent impression of midbrain acoustic fibres may also produce pathological adaptation. Pestalozza and Cloce noted further that hearing loss and pathological adaptation appeared after puncture of the lateral ventricle.

Electro-physiological tests have cast light on the nature of adaptation and its possible anatomical localization Following a strong initial burst the acoustic action potentials gradually decline to a lower level The rate and amount of this decrease or equilibration depends upon the frequency of the stimulus. The decrease continues for 5 to 7 minutes after the start of stimulation. The rate of decrease is at a maximum during the first two seconds (Derbyshire and Davis 1935 Stevens and Davis 1938) These views are supported by the clinical findings of Hood (1950) No changes appeared in cochlear potential amplitude in response to low-intensity stimuli Not until the 95 dB level was exceeded did a fall in amplitude become apparent (Gisselsson and Sørensen 1959) This also was due to fatigue and not to adaptation. In studying the adaptation of action potential Sørensen (1959) observed that a single nerve fibre follows the rule of "all or nothing whereas CM is directly proportional to intensity growth up to 80 dB Adaptation then would seem to be related in the main to the characteristics of the acoustic nerve. Later (1960) Sørensen concluded that a threshold tone-decay test is the functional index of impairment of the central acoustic pathways or of the acoustic nerve Davis (1962) however warns against forming definite conclusions as to the anatomical site of a hearing loss from audiologic tests. T Palva (1964) writes in similar terms Adaptation seems mostly to be associated with retrocochlear deafness. However at present there is no agreement to the values undoubtedly indicating a certain localized pathology

The adaptation test was originally regarded as an indirect method for measuring recruitment However rapid adaptation represents a considerable source of error in recruitment tests In Palva s studies in 1955 14 per cent of the subjects showed a loss of loudness large enough to eliminate recruitment (T Palva 1956) Dix and Hood (1953) and Hood (1955) also found that a recruitment demonstrated with alternating balance may change into the reverse of recruitment when using simultaneous balance (continuous stimulus with simultaneous balancing noise into the other ear) Even though the loudness scale may be apparently narrowed by recruitment it may in actual fact be increased thanks to relapse (rapid strong adaptation) In agreement with the above Ranke (19 4 and Carhart (1957) think that recruitment may

disappear as a result of adaptation. Rapid adaptation, on the other hand may cause difficulty in determining the pure tone threshold. Even Gradenigo (1893 quoted by Reger and Kos 1958) wrote "The functional exhaustibility is often so considerable that the results of the examination by the different methods become so essentially modified that it is impossible if no account is taken of this fact to form an accurate conclusion as to the amount of hearing power present."

The dividing line between normal and pathological adaptation is still today to some extent uncertain. Sorensen (1962) groups the results of the threshold-tone-decay test under three points 1) the threshold remains constant within 10 dB 2) the threshold increases more than 10 dB during three minutes and then remains constant, 3) the threshold increases continuously. In Sorensen's view (1960) adaptation ranging from 0—10 dB is normal and values over 35 dB are clearly pathological. Palva's (1964) observations are within the same limits. "Moderate adaptation during three minutes stimulation of the order of 10 to 30 dB may occur in any type of perception deafness and allows no diagnostic criteria to be made.

The adaptation present in acoustic trauma varied greatly in degree from normal to pathological (Dieroff 1957 Ward, Fleer and Glorig 1961 Glorig 1961 Pestalozza and Cioce 1962 Dieroff and Kowalik 1965). Its amount is not related to recruitment (Ward, Fleer and Glorig 1961) or to the results of Langenbeck's noise audiometry (Dieroff and Kowalik 1965)

F POSTSTIMULATORY FATIGUE

"Fatigue means a decline in activity caused by the previous activity of the organ (Larsen 1953). No clear-cut line of distinction can be drawn between adaptation and fatigue. Fatigue originates from adaptation as a result of a stronger and/or more extended exposure of the ear. While adaptation is a physiological event fatigue is something between physiological and pathological and with added exposure, functional damage is induced (Meyer zum Gottesberge 1954). Adaptation is associated with decreased loudness and fatigue and trauma with loudness recruitment (van Dishoek 1953)

A multitude of methods have been utilized for measuring poststimulatory fatigue, tests of short and long duration, low or high intensity pure tone tests or various noise tests. In the absence of uniform tests there cannot be any normal values (T Palva 1958c). Recently Ward (1967) summarized the different tests and tried them out on one and the same group of subjects. The tests are not comparable. The TTS when due to impulses grows linearly with the exposure time but when due to continuous noise it is logarithmically related to exposure time. This is so at least if the interval between two impulses is sufficiently long (Ward 1963). A burst of 28 shots gave no appreciable TTS whereas 28 single shots produced a broad TTS of as much as 60 dB (Murray and Reid 1946)

The recovery audiogram has the characteristic features of an initially rapid fall towards normal followed by another rise in threshold and a slower drop (Bronstein 1936) Hirsh and Ward (1952) term this second rise the bounce" Hirsh and Bilger (1955) differentiate three typical recovery curves 1) a steep loss even beyond pre-exposure level 2) the bounce and 3) a gradual loss. Davis and his co-workers (1943) have stated that recovery coincides with the exponential curve Recovery from TTS is independent of the way in which TTS was produced (Ward 1960) Comparison of TTS with the pre-exposure threshold shows that the greater the threshold loss the slighter is TTS

The clinical significance of fatigue tests is still at present undetermined. They have been used extensively in trying to separate out noise-susceptibles from normal population It is now generally agreed that fatigue tests do not provide a means of separating out those who are susceptible to noise (van Dishoek 1949 Theilgaard 1951 Davis *et al.* 1953 Larsen 1953 Dieroff 1959 Lehnhardt 1965 etc.) "Susceptibility to acoustic trauma is a trait distributed normally not dichotomously We may speak of high and low susceptibility but not of susceptible against "nonsusceptible ears" (Ward 1967) In addition exposure tests may give rise to permanent acoustic traumata (Davis *et al.* 1950 Theilgaard 1951) Attempts have also been made to apply fatigue tests in differential diagnosis. In critical studies however it is not possible to distinguish by means of the fatigue test the various groups of deafness from one another (Palva 1958b Epstein and Bower 1962) The anatomic locus of the fatigue phenomenon still rests entirely on assumptions Studies on the physiological state of the fatigued ear of guinea pigs showed that the nuclei of the outer hair cells swelled to many times their normal value (Wüstenfeld 1957) Beagley (1965a) calls attention to conductive lesions of the inner ear stating as follows. "The Hensen-Deiter s junction was intact in the severely damaged ears but a large cleft was seen in those ears with little injury and much recovery There is no doubt that a number of mechanical electrical and chemical changes occur in or close to the hair cells in connection with auditory fatigue (Ward 1963) The problem of auditory fatigue is still vexed with uncertainty and controversy' (Ward 1963)

F THEORIES ON THE ORIGIN OF ACOUSTIC TRAUMA

1) THE C_5 DIP

The dip concept was first introduced by Fowler (1929) who defined it as a clear-cut loss in the audiogram, at least 20 dB in depth and not involving more than three octaves another type of dip is an abrupt loss at 4 000 cps or higher which is independent of whether the audiogram is or is not normalized at the higher frequencies The C_5 dip affects chiefly the area round 4 000 cps its maximum is not however necessarily here but quite often at 6 000 cps The maximal dip in particular varies considerably as a

function of time in one and the same individual (van Dishoek 1949) A C_5 dip is a relatively common audiometric finding (Guild *et al.* 1940 Loch 1943 Ciocco 1932)

The C_5 dip is most commonly ascribed to acoustic trauma or skull injury (Uffenorde 1922 Shambaugh 1935 Bunch 1937 Larsen 1939) The borderline between these traumata is diffuse. Ruedi and Furrer (1947) anesthetized the planum mastoideum of their assistants who were then given a few hammer blows behind the ear The sensation created was mainly similar to the sound of a pistol shot. On audiologic examination, a typical temporary C_5 dip was found. Some other factors assumed to play a part in the etiology are intoxications (tobacco and alchohol) certain drugs (cocain and quinine) and more rarely syphilis and retinitis pigmentosa (Larsen 1953) In some cases, however the etiology remains obscure and then it has been customary to regard the dip as congenital or as due to medicines taken by the mother or in early childhood (Guild 1950)

The question as to why and how the C_5 dip arises has stimulated the interest of researchers for well over thirty years. New theories are still being advanced every year which indicates that there is as yet no satisfactory solution to the problem. It has been assumed that the area in the cochlea that corresponds to C_5 is particularly susceptible to trauma. Should the cause lie in special anatomic conditions — in a particular sensitivity of the hair cells — then the C_5 dip ought to be much more common in presbycusis toxic hearing losses etc. (Kraus 1957) Contrary to a number of earlier theories it has been demonstrated that neurovascular disturbances due to loud noise do not affect the internal ear (Rambo Wolff and Freeman 1953 Perlman and Kimura 1962) Ruedi and Furrer thought two oppositely directed pairs of eddies would cause stretching and resulting trauma of the basilar membrane and at the same time of the organ of Corti. The eddies change direction at about 4 000 cps thus producing the C_5 dip Objective demonstration of the two pairs of eddies has not proved possible however Owing to resonance in the external auditory canal and the mastoid antrum the sound wave amplitude increases about 20 dB between 2 000 and 3 500 cps compared with the waves at other frequencies (Onchi 1951) This might be a factor in the production of the C_5 dip Hilding (1953) and Kraus (1957) account for the C_5 dip on the basis of the fluid flow and pressure set up by stapedial movement and acting on the border between the straight and spiral portions of the cochlea (this area responds to 4 000 cps stimuli) The dip therefore would be due to a hydrodynamic phenomenon elicited by a sound impulse which phenomenon grows more marked with increased intensity of sound and always affects one and the same portion of the cochlea regardless of the frequency duration and intensity of the stimulus.

According to most recent reports the points to which chief attention should be directed when studying the pathogenesis of the C_5 dip are the stimulus itself its frequency spectrum and intensity (Lehnhardt 1965) A factor worth considering is the maximal sensitivity of the ear at 1 000—4 000

cps attributable to hydrodynamic causes (von Békésy 1960) As a result of pure tone stimulation the TTS spreads asymmetrically mainly to frequencies higher than the stimulus (Davis *et al.* 1943 Hood 1950 Hirsh and Bilger 1955) When recording the TTS curves resulting from several pure tones in the same diagram the summation occurs at or above 4 000 cps The sensitivity of the ear however decreases steeply after 4 000 cps. Thus it is exactly the area round 4 000 cps where the maximum effect occurs (Lehnhardt 1965) The greater the intensity the higher are the frequencies reached by maximal TTS (Wegel and Lane 1924 Nakamura 1964) Indeed Lehnhardt says the dip occurs at about 6 000 cps if the sound stimulation is very loud. At somewhat weaker intensities the dip affects 4 000 cps or even lower frequencies The dip always develops in the range corresponding to the portion of the basilar membrane affected by maximal sound stimulation (Lehnhardt 1965)

2) PRESBYCUSIS — SOCIOCUSIS — ACOUSTIC TRAUMA

Disregarding diseases proper the causes of inner ear deafness can be divided into three main groups 1) physiological changes due to aging, or presbycusis 2) changes due to noise in the social environment (environmental noise) or sociocusis and 3) acoustic trauma due strictly to the occupation Presbycusis and sociocusis are generally placed under the joint heading 'nonoccupational hearing loss that accompanies age (Glorig 1958) In single cases it is impossible to make a distinction between these three factors affecting the hearing. Indeed such a separation has not even been aimed at in the majority of pathologic anatomical and audiologic studies performed.

In the opinion of Glorig (1958) the term presbycusis should be restricted to hearing loss due to physiological changes associated with aging. Schuknecht (1955) described this presbycusis as being due to degenerative changes originating in the basal part of the cochlea extending towards the apex and affecting almost simultaneously and equally the various structures in the cochlea and in the afferent and efferent nerve fibres. Later (1964) Schuknecht divided presbycusis into four types 1) sensory 2) neural 3) metabolic, and 4) mechanical Sensory presbycusis is characterized by atrophy of the organ of Corti in the basal end of the cochlea and auditory nerve and typified by abrupt high tone hearing loss. The neural type appears as poor speech discrimination but not until advanced age being a result of loss of neural population in the auditory pathways. Metabolic presbycusis is a slowly progressing sensori neural hearing loss manifested functionally as a flat audiogram The only microscopic sign is atrophy of the stria vascularis Possibly the stria vascularis is essential to the maintenance of the bioelectric and biochemical properties of the endolymph. The disturbance then consists in defects in the physical and chemical processes by which energy is produced and made available for use by the sense organs. High adenosine phosphatase (enzyme) activity has been shown by electronmicroscopy in the stria vascu-

laris (Nakai and Hilding 1966) On the other hand injections of adenosine triphosphate have reduced fatigue greatly (Faltynek and Vesely 1964) Mechanical presbycusis might be referable to stiffening of the basilar membrane or some other disorder in motion mechanics of the cochlear duct. Light microscopic studies have failed to reveal any cytological changes in the cochlea or auditory nerve The functional manifestation of mechanical presbycusis is a descending audiometric curve.

According to von Békésy's (1960) hearing theory based on the hydrodynamics of the inner ear each frequency of the sound stimulus creates a travelling wave on the basilar membrane. The position of the maximum amplitude of vibration of the basilar membrane is determined by the frequency of the stimulating sound waves. Tasaki (1954) using a microelectrode technique showed in guinea pigs that the basal turn responds to practically all frequencies within audible range whereas the upper portions of the cochlea respond only to low tones. On this basis Meyer zum Gottesberge (1955) states that the acoustic load affects chiefly the basal end of the cochlea. Accordingly presbycusis would be a product of age and the consequence of inner ear consumption by the act of hearing itself Rosen *et al.* (1964) consider that there are other factors in addition to noise which may contribute significantly to presbycusis e.g. nutrition genetics tissue changes climate and stress and strain These theories however are not designed to differentiate presbycusis from sociocusis. They seem rather to concern the mechanism of onset of sociocusis

Rosen *et al.* (1962 1964) wished to study audiologically a population in which loss of hearing could be ascribed to physiological aging. They chose the Mabaan people in the Sudan who still live in a practically noise-free environment. The control series consisted of city populations from New York, Düsseldorf and Cairo. The deafness in the case of the control populations was made up of two components presbycusis and sociocusis. Comparison of the results showed that sociocusis affected hearing to a much greater extent than did the aging process alone. A number of other audiological studies concerned with the influence of age on hearing (Bunch 1929 Leisti 1949 Jatho and Heck 1959 Johansen 1943 Glorig *et al.* 1957) have dealt with presbycusis and sociocusis jointly However their titles often, wrongly refer to presbycusis alone. The average age correction values of the various studies differ to some extent. This might be due to differences in the respective social environments in other words in the number and nature of the factors playing a part in sociocusis.

In practice the borderline between sociocusis and acoustic trauma may be just as diffuse as is that between presbycusis and sociocusis. Traffic noise in towns and the noise level inside a car can exceed the critical 90 dB level considerably even up to 115 dB (Lehnhardt 1965) There are a great number of other situations in which the ear is temporarily exposed to hazardous noise levels Their effect on hearing is hard to estimate, and so there appears in many studies of presbycusis (Bunch and Rainford 1931

cps attributable to hydrodynamic causes (von Békésy 1960). As a result of pure tone stimulation the TTS spread asymmetrically mainly to frequencies higher than the stimulus (Davis *et al.* 1943, Hood 1950, Hirsh and Bilger 1955). When recording the TTS curves resulting from several pure tones in the same diagram, the summation occurs at or above 4000 cps. The sensitivity of the ear however decreases steeply after 4000 cps. Thus it is exactly the area round 4000 cps where the maximum effect occurs (Lehnhardt 1965). The greater the intensity, the higher are the frequencies reached by maximal TTS (Wegel and Lane 1924, Nakamura 1964). Indeed Lehnhardt says the dip occurs at about 6000 cps if the sound stimulation is very loud. At somewhat weaker intensities the dip affects 4000 cps or even lower frequencies. The dip always develops in the range corresponding to the portion of the basilar membrane affected by maximal sound stimulation (Lehnhardt 1965).

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Disregarding diseases proper, the causes of inner ear deafness can be divided into three main groups: 1) physiological changes due to aging or presbycusis, 2) changes due to noise in the social environment (environmental noise) or sociocusis, and 3) acoustic trauma due strictly to the occupation. Presbycusis and sociocusis are generally placed under the joint heading "nonoccupational hearing loss that accompanies age" (Glorig 1955). In single cases it is impossible to make a distinction between these three factors affecting the hearing. Indeed such a separation has not even been aimed at in the majority of pathological-anatomical and audiological studies performed.

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gauge is good, its linearity varies ± 0.5 per cent. A power indicator mounted at the measuring site transforms the mass pressure into an electrical phenomenon which is conducted into the Kistler pressure gauge and further into a co-ordinate analyser which registers the pressure. This is recorded by tele autograph.

For spectrographic analysis the reports were recorded with an UHER tape recorder having a linear reproduction curve for the frequencies concerned. From the tape recorder the reports were transmitted direct into a sound spectrograph "SONA-GRAPH (manufactured by the Kay Electric Company Pine Brook, N Y) This apparatus analyses sound within the range 80—8 000 cps The sound is recorded on the magnetic drum of a rotating disk from where it can be reproduced on to a nonphotographic, electrically sensitive and facsimile type paper

METHODS OF INVESTIGATION

1) PRELIMINARY STUDIES

Questionnaires were distributed to the entire regular personnel in an effort to discover possible earlier ear diseases and other factors that might have affected the hearing. Questions as to certain subjective symptoms thought to be characteristic of noise injuries were included. An attempt was also made to determine the time of onset of hearing loss the number of shots fired with various weapons as well as the part played by possible skull injuries and civilian occupation in hearing.

Medical NCOs specially trained for the task made the preliminary hearing tests based on the screening principle. The threshold level was +10 dB and testing frequencies were 250 500 1 000 2 000 3 000 4 000 6 000 and 8 000 cps. If a subject failed to hear one (or more) of the test frequencies pure tone thresholds were recorded in the usual way In the screening tests only air conduction was tested and no masking was used in the other ear

2) AUDIOLOGIC STUDY

All subjects with a pathological finding in the screening tests were asked to present themselves for extension tests which were invariably performed by the investigator in person.

Early spring (1963) was chosen for the purpose at that time of the year there were no shooting camps and those taking a special interest in shooting were not yet allowed into the shooting ranges. In the case of almost all test subjects, therefore, months had passed since they had last been shooting These measures were taken to ensure that the acoustic trauma discovered was of permanent character Each subject was given an otorhinolaryngological

examination designed to reveal any possible middle ear disease that mi ht have affected the hearin Weber and Rinne tests with the C_2 f rk were made The blood pressure of each subject was regi tered Then f llowed s me more detailed audiol gic tests

Testing was invariably started by re rding a pure tone audiogram f r the better ear of the subjects (all had had a preliminary hearing test) u ing a short stimulus (c 1—1½ sec) an l a so called c ntinued threshold deter mination technique (Hirsh 1952) Masking wa d ne w th white noise ranging in effective level from 50 to 70 dB The procedures recommended f r instance by T Palva (1954 1954d 1957) were f llowed in maskin The thresholds were recorded at 250 500 1 000 1 500 000 3 000 4 000 6 000 8 000 and 12 000 cps In the same way bone conduction thresh lds were rec rded f r the frequen cies 250 500 1 000 1 500 2 000 4 0) and 6 000 cps

It could be assumed n the basi f the preliminary test and com parisons with the results f previous studies on AT that there would be mainly three different types f audi ram (F) Thi divi n was utilized when determining the frequencies t be tested in m re detail especially when tudying loudness recruitment per timulatory adaptati n and post stimulat ry fatigue

For determining possib e recruitment the direct monaural test (Reger 1936) between two frequencies (so-called Reger test) was almost exclusively employed In only a few special cases use was made of the direct binaural test described by Fowler (1936) Th e test frequencies were chosen a follow The frequency A (Fig) at which the pure tone threshold was normal or nearly normal was taken a reference If allowed by the degree of AT recruitment wa as far as pos ible determined at three frequencies Testing

Fig 2 T re l pu t n a d re am t) dip (Capta n 38 ea)) divided d p Se gment 5 a) 31 ab upt (5 g nt l l la 47 sed s)

was always started at frequency I (Fig. 2) because from the point of view of the subject being tested its interpretation would seem to be easiest here. Equal balance was determined as far as possible at 5—20 dB intervals and up to 100 dB Duration of stimulus averaged 1—1½ sec. and the interval between stimuli about ½ sec.

A perstimulatory adaptation (threshold-tone-decay) test was made at the same frequencies I II III (Fig. 2) as used in testing recruitment This test consists in listening to a soft sound as long as possible but so that the tone must be distinct throughout and not imagined. The test was always started at the highest frequency (III) to avoid the possible fatigue phenomenon in testing the other frequencies. On disappearance of the test tone intensity was increased in 5 dB steps until the subject heard an uninterrupted tone for at least a minute (total duration of test not less than 3 minutes) or until the loudest tone obtainable from the audiometer at the frequency concerned disappeared. To avoid fatigue, the left and the right ear were always tested in turn, and a rest period of at least 5 minutes was allowed between two adaptation tests on the same ear When required white noise was used to mask the contralateral ear If the subject tested did not hear the cutting off of the tone at the end of the session the test was repeated. In the course of the study it appeared that subjective changing of the test tones was a very common feature during adaptation and therefore part of the subjects were tested as to whether the sound was heard as a pure tone or as a buzzing soughing or wave-like sound

Poststimulatory fatigue was determined by checking the pure tone threshold, after the adaptation test at 15 sec. intervals until threshold was restored to normal.

A so-called articulation score was determined for each subject by speech audiometry Discrimination ability was tested at an intensity about 30 dB louder than the speech threshold. There were 30 test words two- or three syllable Finnish words in common use, for each ear The intensity at which the subject heard correctly 50 per cent of the words was taken as speech threshold. The speech unit of the audiometer was so calibrated that the average threshold of the speech range of the pure tone audiogram (500—1 000—2 000 cps) and the recorded speech threshold are on the same level. If necessary white noise was used for masking according to universally accepted principles in audiometry

3) ELIMINATION OF HEARING LOSS ACCOMPANYING AGE

An evaluation of the effect of age on hearing must include both presbycusis and sociocusis. The age correction curve in the present study is based on the 1954 Wisconsin State Fair Hearing Survey "nonoccupational hearing loss that accompanies age (Glorig *et al.* 1957) The values for 250 and 8 000 cycles are from Johanssen's (1943) report since these particular frequencies were

Table 3

Correction (in dB) for changes due to presbyacusis in the various age groups

age in years	250	500	1000	1500	2000	3000	4000	6000	8000	[illegible]
20–29	0	0	0	0	0	0	0	1	3	4
30–39	1	1	1			5	5	6	8	10
40–49	4		3	4		11	1	13	14	47
50–59		5	6	8	1	11	[illegible]	1	[illegible]	50

not tested in the survey reported by Glorig *et al.* and since for the other frequencies the values of Glorig *et al.* and of Johansen are approximately equal. The correction values for 1 000 cps were calculated on the basis of the studies of Rosen *et al.* (1964) and Jatho and Heck (1959). Table 3 gives the averages for the physiological hearing loss associated with age at each frequency and in the various age groups.

ANALYSIS OF THE REPORTS

Recording of reports on magnetic tape took place under field conditions to preclude reflexes from walls, woods, etc. The reports were recorded at the firer's position. From the tape recorder the sound of the report was transferred by a connecting wire direct into the spectrograph, where the sound was recorded on the magnetic drum of a rotating disk. The sound could be reproduced on the electrically sensitive paper. For determining the spectrum of the report use was made of a narrow filter which analysed the sound in 45 cps bands. An intensity curve was determined in connection with the basic sonagram depicting the relative intensity of the report as a function of time. In addition, a sound spectrum analysing the sound accumulated in 5 msec as a function of the various frequencies and intensity was determined at two or usually three points of the report.

Captain R. Sihvola measured the sound pressure and duration of the reports at the Testing Station using the equipment described above. These measurements too were performed under field conditions to exclude reflexes and other possible sources of error.

STATISTICAL TREATMENT

The statistical treatment of the present material was carried out by statistical routine methods in general use (Documenta Geigy, Wissenschaftliche Tabellen).

The χ^2 test was used for comparison of the dependence of various factors in pairs. An observation was distributed according to two criteria of classification A and B according to A into k classes and according to B into l classes. When the total number of individuals included in categories A_i and B_j are marked a_i and ${}_j$ the formula $a_i\ {}_j/n = \bar{}_{ij}$ gives the so-called independence figures. For each test the entity $\chi^2 = \sum_{i=1}^{k} \sum_{j=1}^{l} (a_{ij} - \bar{a}_{ij})\ \bar{a}_{ij}$ was calculated. The assumption that A and B are independent was refuted if χ^2 exceeded the χ^2_p corresponding to the degree of freedom $f = (k-1)\ (l-1)$ The probability of error is then smaller than p The difference has been considered significant if $0.01 < p = \leq 0.05$ highly significant if $0.001 < p \leq 0.01$ and very highly significant if $p \leq 0.001$

IV. RESULTS

[illegible]

The preliminary tests included 4?? army regular personnel among them 106 officers. According to the screening test 14? of these had normal hearing, the number including 42 officers. A probable acoustic trauma was present in 241. Changes in hearing due to some other ear lesion were found in 41 subjects. The series to be subjected to closer examination studies consisted of 19. Table 4 shows the distribution of subjects with normal hearing, with AT and with other ear pathology by units. In the group of AT there were 9 subjects with AT in one ear and conductive hearing loss in the other.

The group of other ear lesions included among others two perceptively deafened subjects. One of these had a typical "basin-shaped" audiogram (Fig. 3). However, since this subject's father also showed a similar feature in the audiogram this case was not accepted into the AT series but considered most probably as hereditary deafness. The other case, a senior sergeant aged 34, had noticed gradual impairment of hearing during the summer of 196? (Fig. 4). Because the hearing impairment was not, however, distinctly related to acoustic exposure, this case was also excluded.

The series was classified by age and years of service. Tables 5 and 6 compare the distribution of normally hearing subjects and cases of AT in the various groups. The results indicate that the increase in AT is very highly significant as a function of age and of years of service. Figure 5 presents, expressed as percentages, the growth of the AT component in the various age and duration of service groups as compared with normally hearing subjects.

Table 4

Subjects with normal hearing, AT and other lesions of the ear classified by units of Defence Forces

Unit	Total	Normal hearing		AT		Other lesions of the ear
Field artillery	14?	3?	2?.4	101	68.7 %	14
Coast artillery	61	?0	3?.8	3?	54.0 %	8
Antiaircraft artillery	44	19	43.2	19	43.?	6
Field artillery Supply unit	37	11	?9.7 %	21	56.8	5
Testing station	21	6	?8.6	1?	57.1	3
Infantry	111	51	46.0	55	49.5 %	5
Total	4?2	140	33.2 %	241	57.2 %	41 9.6 %

Fig. 3.

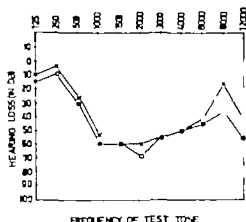


Fig. 4

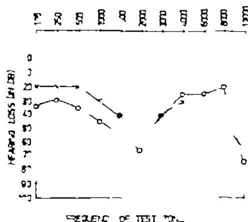


Fig. 3. Audiogram of 27 year old sergeant (See text) x=left ear o=right ear Bone conduction = air conduction in this audiogram and later ones unless other wise stated.

Fig. 4 Audiogram of 34-year old senio sergeant (See text)

Table 5

Distribution of subjects with normal hearing and with AT according to age.

Age in years	Normal hearing	AT
20—29	61 61.6 %	38 38.4 %
30—39	39 41.5 %	55 58.5 %
40—49	31 26.3 %	87 73.7
50—59	8 32.0 %	17 68.0

Table 6

Classification of subjects with normal hearing and with AT according to duration of service.

Years of service	Normal hearing	AT
0—5	50 66.7 %	25 33.3 %
6—10	29 50.9 %	28 49.1 %
11—15	21 36.2	37 63.8 %
16—20	15 30.6 %	34 69.4 %
over 20	4 24.7	73 75.3 %

2) ANAMNESTIC DATA

On the basis of the pure tone audiometric finding, the subjects with AT were classified by degree of severity using criteria to be defined later in this study Table 7 gives briefly the subjective symptoms considered typical of AT in subjects with normal hearing and with AT of various degrees These

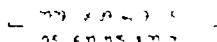


Fig. 5. Proportion ... ted ... b... acoustic trauma in various age and duration of service groups. Re... given ... percentages in relation to normally hearing subjects.

classical symptoms occur very commonly in normally hearing persons also. It should be taken into account in studying the subjective symptoms of hearing loss (Table 7) that age corrections were applied when estimating the degrees of severity. This being so, it may be that even in slight hearing impairment the trilling of a cricket, the ticking of a watch or the ring of the telephone bell may be missed owing to presbyacusis adding its contribution to the hearing impairment from AT. In fact, nearly all subjects in this group were over 40—50 years.

Other possible factors in hearing loss are presented in Table 8. A history of otitis and signs indicating otitis were interpreted as previous ear disease. The group of AT included 3 subjects who had undergone mastoidectomy. They had normal eardrums, bone and air conduction curves coincided, and there was a typical pronounced dip which did not differ in any way from the other audiologic findings. Fifteen subjects in this group had a history of skull injury, nine of these could be regarded as cerebral concussion and six resulted from splinter wounds sustained in the war. From this series it appears that only 32.2 per cent of the regular personnel taking part in the Fenno-Russian wars 1939—1944 had retained normal hearing.

The previous civilian occupation could only in 6 cases have affected the development of AT (6/197). Four of these cases can even be regarded as probably partial civilian trauma, the subjects concerned had worked as boiler makers in a shipyard for 2 to 6 years. However, seeing that the clinical

Table 7

Some symptoms in subjects with normal hearing and in AT of varying degrees. Results expressed as percentages.

Symptom	Normal hearing	Grades of severity of AT I	II	III	IV
Tinnitus	15 7	32.6	24.8	34 7	56.0
Tinnitus after firing	40.7	48.8	48.6	56 7	64.0
Discomfort caused by any noise	25.0	34.9	41.3	42.8	52.0
Subjective impairment of hearing	12.3	16.3	30.3	62.0	100.0
Trilling of cricket not heard	0	16.3	23.9	42.8	56.0
Ticking of wrist watch not heard	0	13.9	18.3	39.0	84.0
Telephone bell not heard	0	4 6	5.5	21 4	44.0

Table 8

Certain anamnestic data on subjects with normal hearing and with AT of varying degrees. Results expressed as percentages.

Symptoms	Normal hearing	Grades of severity of AT I	II	III	IV
Previous otitis	23.6	4.6	3.7	6.4	4 0
Skull injuries	10.7	2.3	10.1	10.7	8.0
Active service during war	32.2	41.9	50.5	60.4	80 0

pattern of their AT did not differ from the average finding in the rest of the series they also were included.

In 93 4 per cent of those studied, the development of AT was slow unnoticed and extended over several years so the trauma could be assumed to be chronic. When asked about the time of onset of the hearing loss only 13 (6.6 per cent) stated that hearing had deteriorated abruptly in connection with some special event Some of these subjects are more closely considered below as special cases The cause of AT in 9 cases was an explosion occurring close by In 2 cases there was a similar situation cannon blast in close proximity to the ear One subject working at the Testing Station reported that hearing was impaired "fairly" quickly in connection with shooting to test the durability of mortar barrels. There was one additional case of rapid deafening this subject was wounded by a pistol shot in the right temporal region. Only one of the suddenly deafened subjects had definitely sustained a ruptured eardrum.

It proved impossible to estimate the number of rounds of shot fired since each subject had to shoot with several types of weapon every year and the number of shots vary widely Those included in the AT group definitely did more shooting than the normally hearing.

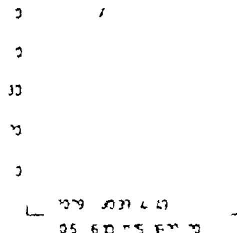


Fig. 3. Proportion accounted for by acoustic trauma in various age and duration of service groups. Results given as percentages in relation to normally hearing subjects.

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Table 11

Mean audiogram values in various age groups. Corrections for age and calibration applied. Left ear

Age		250	500	1000	1500	2000	3000	4000	6000	8000	12000
	Q_3	−3.5	−3.0	−1.5	2.0	6.5	−0.5	9.0	14.5	5.0	−17.6
20—29	Q_2	2.0	2.7	1.1	5.3	12.5	16.2	44.2	48.3	41.5	20.2
	Q_1	9.6	9.0	8.1	14.4	29.4	42.6	74.2	76.4	78.5	50.7
	Q_3	−3.9	−2.5	−1.5	−0.7	2.2	−1.0	7.0	15.4	20.4	−13.2
30—39	Q_2	2.1	2.7	1.0	5.9	12.6	11.1	39.6	48.6	45.4	14.7
	Q_1	7.5	6.4	8.5	17.6	41.5	52.2	70.5	79.6	75.3	40.6
	Q_3	−5.3	−2.5	−4.2	−1.7	−0.4	−6.1	5.8	18.9	15.6	−2.6
40—49	Q_2	−2.5	3.3	0.7	3.3	10.2	16.3	38.2	47.4	47.8	26.6
	Q_1	7.6	9.5	8.7	16.3	44.4	47.1	63.9	66.8	75.9	43.7
	Q_3	−7.0	−1.5	−5.2	−4.2	−3.2	−4.0	10.7	14.2	17.7	−5.2
50—59	Q_2	1.1	3.5	−0.9	2.6	0.1	15.1	40.1	43.0	49.4	18.5
	Q	9.0	8.0	8.5	18.3	35.5	51.0	60.8	60.5	56.5	28.5

Table 12

Mean audiogram values of AT analysed by years of service. Corrections for age and calibration applied. Right ear

Years of service		250	500	1000	1500	2000	3000	4000	6000	8000	12000
	Q_3	−3.3	−2.2	−2.0	1.0	4.5	3.3	13.5	20.3	7.3	−16.5
0—5	Q_2	2.9	3.0	1.4	6.3	10.8	14.9	43.3	56.8	43.9	22.0
	Q	10.0	7.0	7.2	14.3	22.9	42.5	73.1	81.2	85.7	90.5
	Q_3	−1.2	−0.9	−2.4	0.9	8.8	2.6	13.5	16.0	7.6	−12.0
6—10	Q_2	4.1	3.6	1.2	5.4	15.5	15.7	38.7	53.1	40.6	26.8
	Q_1	10.3	10.5	9.0	12.3	26.1	41.1	71.4	77.4	71.1	50.2
	Q_3	−0.9	0.6	−1.9	2.6	3.8	−2.2	2.7	25.6	24.3	1.3
11—15	Q_2	3.0	3.5	1.6	5.1	11.7	9.7	36.0	56.7	54.0	22.3
	Q_1	9.1	10.6	10.6	18.3	38.1	61.5	77.1	85.0	82.4	51.8
	Q	−4.4	−2.8	−1.3	0.3	4.3	−0.1	4.1	20.0	15.7	−6.0
16—20	Q_2	3.8	3.8	2.2	7.2	15.0	12.4	38.4	48.7	53.6	31.3
	Q_1	11.5	8.9	7.9	11.1	63.1	72.4	81.5	79.7	79.0	45.6
	Q_3	−2.4	−1.5	−3.7	−1.3	3.1	−2.3	11.9	23.4	23.8	2.4
over 20	Q_2	2.6	4.9	2.2	5.5	12.3	17.7	41.8	54.7	53.6	27.8
	Q_1	10.4	11.6	10.1	19.4	45.5	57.5	67.0	73.5	75.5	85.0

The average hearing loss due to AT are classified by age and years of service in Tables 10 11 12 13 and 14 All three audiometric types are represented but no special cases In calculating the values regard was had to the age correction and to audiometric calibration correction The tabulated values include the first (Q_1) second (Q_2) and third (Q_3) quartiles the first quartile (Q_1) the average hearing loss of the poorest 25 per cent of the hearers Q the median and Q_3 the best 25 per cent of the hearers respectively Comparison of Tables 10 and 11 shows that in AT no further

Table 13

Mean audiogram values of AT analysed by years of service Correction for age and calibration applied. Left ear

		250	500	1000	1500	2000	3000	4000	6000	8000	12000
	Q	—5 6	—4 8	—3 8	0	3 3	—1 0	4 5	1 5	2	—18 0
0—5	Q	0 7	1 7	—0 4	3 5	8 6	8 1	37 3	43 5	31 7	18 7
	Q	7 2	6 9	5 4	1 5	30 4	35 1	77 7	73 8	74 9	44 3
	Q	— 7	—1	—1 0	0 6	8	—0 1	11	13 3	9 3	—17 7
6—10	Q	3	3 0	6 7	4 4	14 3	16 3	41 3	45 9	47 4	17 3
	Q	8 8	8 8	9 0	15 0	31 1	40 7	65 6	77 4	78 5	43 2
	Q	—4 2	—0 5	— 4	—1 1	—0 3	—1 2	4 6	17 7	18 5	—15 1
11—15	Q	0 7	3 2	1 0	5 1	9 4	8 1	37 0	43 1	55 3	16 9
	Q	10 1	9 6	13 9	19 1	39 8	43 9	66 9	6 1	69 4	44 7
	Q	—3 2	—3 6	—0 5	0 1	0 8	— 0	9 7	20 9	17 8	—9 7
16—20	Q	1 5	3 0	1 7	6 1	11 7	13 4	39 0	50 9	44 7	21 4
	Q	6 9	7 3	4 7	13 6	5	59 5	63 1	6 8	71 6	38 9
	Q	—6 7	— 8	—5 3	—2 8	—1 3	—4	7 8	23 8	17	1 3
over 20	Q	—0 4	3 4	—0 1	3 7	11 3	20 6	43 0	56 9	50 1	8 3
	Q	7 6	8 7	9 5	18 8	4 5	53 9	68 0	74 7	74 5	4 3

Table 14

Mean values of AT Corrections for age and calibration applied

Left ear	250	500	1000	1500	2000	3000	4000	6000	8000	12000
Q	—4 7	—2 6	—3 0	—0 8	1 6	—3 3	7 3	16 6	14 7	—9 0
Q	0 1	3 0	0 7	4 4	11 0	14 7	40 0	47 5	46 0	21 1
Q	8 1	8 3	8 3	16 5	39 7	48 1	67 7	72 1	74 3	42 8

Right ear	250	500	1000	1500	2000	3000	4000	6000	8000	12000
Q	—2 8	—1	—2 8	—0 1	4 3	—0 6	9 7	22 0	18 1	—5 1
Q	1 2	4 0	1 8	5 9	13 0	14 3	40 4	54 0	50 6	22 6
Q	8 5	10 1	9 0	16 0	40 9	56 1	72 1	78 3	77 7	48 9

impairment with age is to be expected. Tables 12 and 13 analyse the development of AT as a function of years of service. The results indicate that AT reaches its definitive permanent stage rapidly probably within five years of service

Using the same statistic dispersion method mean hearing loss curves for the left and right ear separately were calculated for the total material (Table 14 Figs. 6 and 7) and, for a better overall picture average curves for both ears and average curves for the total material (Table 15) The AT affecting the right ear is statistically significantly greater than the one affecting the left ear On comparison of the mean values for the left and right ear in Table 14 the differences are found to be very slight and in practice AT may be considered more or less symmetrical in the two ears. This appears even more distinctly from a study of the individual audiograms. Allowing for a 5 dB error due to measurement technique 56 7 per cent had a symmetrical hearing loss 21.5 per cent had a poorer left ear and 21.8 per cent had a poorer right ear

For greater convenience the series was divided by degree of severity as follows

- Grade I incipient lesion, narrow dip maximum loss 30 dB
- Grade II depth of dip 30—60 dB The dip is required not to extend to the speech range (500—2 000 cps)
- Grade III according to mean curves the so-called permanent level is reached. The dip is over 60 dB deep and/or extends to speech range.

Fig 6

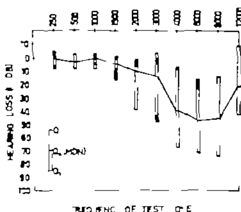


Fig. 7

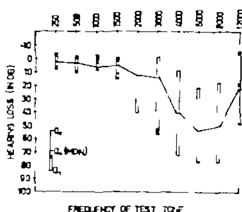


Fig 6 Average hearing loss in total series. Corrections for age and calibration applied The first quartile (Q) the second quartile (Q) and the third quartile (Q) are presented to show the hearing loss of the poorest 25 per cent of the hearers the median and the best 25 per cent of the hearers respectively Left ear

Fig 7 Average hearing loss in total series. Corrections for age and calibration applied. The first quartile (Q) the second quartile (Q) and the third quartile (Q) are presented to show the hearing loss of the poorest 25 per cent of the hearers the median, and the best 25 per cent of the hearers respectively Right ear

Grade IV there is a loss also at the low frequencies (500—1 000) cps

The series including the special cases was dealt with in accordance with this classification It is found when comparing the occurrence of hearing loss of different degrees in the various age groups as already indicated by Tables 10 and 11 that with advancing age the number of severe cases does not increase to any statistically significant extent (Table 16)

To illustrate the development of AT Table 17 depicts the position of the maximum dip i e the mean frequency where the loss is greatest in the various duration of service groups The abrupt type was not included since it was likely to "improve" the results A frequency corrected for audiometer calibration was used when determining the mean frequency (Table 2) As AT progresses the maximum dip remains at about 5 500 cps all the time In other words the dip deepens and widens as the injury increases

Table 15

Average curves of AT Corrections for age and calibration applied All age groups and audiogram types included (no special cases) Frequencies adjusted to nearest full 100 Values expressed in dB

	250	500	1000	1500	2000	3000	4000	6000	8000	12000
Left	0.9	2.9	1.7	6.1	15.9	18.6	35.7	45.9	45.3	19.0
Right	3.1	4.3	2.5	7.1	15.[illegible]	[illegible]1.6	41.0	5[illegible].3	49.5	[illegible]5
Both	2.0	3.6	[illegible]1	6.6	17.0	20.1	39.8	49.1	47.4	20.7

Table 16

Occurrence of various grades of AT by age groups.

Grades of severity	Age groups 20—29	30—39	40—49	>50
I	15	12	14	2
II	23	31	48	7
III	33	58	76	20
IV	2	5	14	4

Table 17

Mean frequency affected by maximum loss in various duration of service groups.

Years of service	left ear	right ear	both
0—5	5404	5326	5464
6—10	5731	5223	5498
11—15	5897	5669	5791
16—20	5291	5534	5418
over 20	5052	5599	5326
Total			5483

In Table 18 are shown the results of testing of recruitment function in AT at various frequencies (cf Fig 2) using the Reger test and, exceptionally the Fowler test In the great majority of cases there was recruitment complete or incomplete in all audiogram types. Taking into account all frequencies tested and all audiogram types loudness recruitment occurred in over 90 per cent. Incomplete recruitment was surprisingly common. The absence of recruitment phenomenon relatively more frequently at frequency I is accounted for in part by the slight hearing loss (cf Figs 6 and 7) and on the other hand, also owing to the slight loss the changes accompanying age are relatively greater at frequency I compared with the others. One of the subjects a senior sergeant 30 years of age with dip type hearing loss showed the reverse of recruitment at frequency I (incomplete recruitment at other frequencies)

In general the changes due to AT are maximal at frequency II Comparison, at this frequency of the function of the recruitment phenomenon in various grades of AT (Table 19) indicates that the slighter the AT the greater is loudness recruitment and, conversely the greater the AT the less is loudness balance. *This inverse ratio is very highly significant (v.h.s.) statistically*

Table 18

Recruitment-phenomenon in various audiogram types at frequencies I II III Both ears. Results expressed as percentages.

	I Frequency	II Frequency	III Frequency
	"DIP"		
Overrecruitment	3.8	4 7	4.5
Complete recruitment	*40.5*	*46.5*	*38.9*
Incomplete recruitment	44.5	45.3	53.1
No recruitment	11.2	3.5	3.5
	"DIVIDED DIP"		
Overrecruitment	2.7	0	2.9
Complete recruitment	54.0	40.5	41.2
Incomplete recruitment	24.3	43.3	53.0
No recruitment	19.0	16.2	2.9
	ABRUPT"		
Overrecruitment	0	4.1	0
Complete recruitment	30.6	28.6	6.2
Incomplete recruitment	49.0	63.2	84 4
No recruitment	20 4	4 1	9 4

Adaptation was divided into three groups using Sorensen's (1962) classification. *The increase in amount of adaptation is in direct proportion to the magnitude of AT*, the difference being highly significant. The result was calculated at frequency II where the hearing impairment was maximal (Table 20). Mean adaptation at frequency I was 13.58 ± 10.20 dB, at frequency II 17.54 ± 9.30 dB and at frequency III 18.04 ± 8.85 dB. Sorensen's third type in which there is continuous tone decay and a permanent level is not reached within the audiometer range was not included. This third type of adaptation occurred at frequency I in 1.4 per cent of the subjects, at II in 10.8 per cent and at III in 22.2 per cent. Even in one and the same ear the amount of adaptation can vary between type I and type III, though as a rule adaptation is of approximately similar type at all frequencies. It only increases in amount as the frequency grows higher.

In a number of cases adaptation was very marked during the first few seconds and could then decrease as much as 20—25 dB. In these same cases the determination of the pure tone threshold often presented difficulties. Adaptation also frequently made the testing of loudness balance difficult. During tests for recruitment the subject under study often said himself that the stimulus was lacking in sharpness and as if it were faded rapidly. In testing recruitment it was necessary in these cases to use a shorter tone stimulus than ordinarily, which of course affects the results to some extent. There is no statistically significant correlation between recruitment and adaptation.

Table 19

Recruitment function in various grades of AT. Results expressed as percentages

Recruitment	Grades of severity I	II	III	IV
Overrecruitment	16.7	4.9	1.1	4.0
Complete recruitment	45.2	46.6	47.7	16.0
Incomplete recruitment	33.3	43.6	51.7	60.0
No recruitment	4.8	4.9	4.5	20.0

Table 20

Types of adaptation in AT of varying degree. Results expressed as percentages

Adaptation type	Grades of severity I	II	III	IV
I	33.3	27.2	4.4	28.0
II	66.7	68.9	59.1	48.0
III	0	3.9	16.5	24.0

even though there is a distinctly observable trend (nearly significant) the greater the adaptation the less is loudness recruitment. Table 21 summarizes the adaptation values obtained in all the audiogram types at each frequency studied, and compares them with the various recruitment groups.

Sorensen's type III adaptation is considered definitely pathological and so is type II if it exceeds 30 dB. Of those included in the group of over recruitment 5.6 per cent had pathological adaptation, in complete recruitment the corresponding figure was 11.5 per cent, in incomplete recruitment 19.7 per cent, and in nonrecruiting cases 14.4 per cent. Type III seems to be associated mainly with incomplete loudness recruitment or nonrecruiting deafness.

Diplacusis

During adaptation the test tone often changed subjectively in nature from a clear continuous ringing to a wave-like buzzing or humming tone or into a vague murmuring. This diplacusis is analysed in Table 22. Since there were no statistically significant differences at frequencies I, II and III all the frequencies were included in the table. At the early stages of the study all subjects were not asked about subjective changing of the tone and therefore only a part of the series appears in the table. Measurement of tones heard as a clear ringing tone and on the other hand, altered sounds using the tone decay principle may reveal even considerable differences (Fig. 8) and the result may change from normal to pathological. Throughout this work, testing for adaptation has been based on "hearing the sound". No association between diplacusis and some definite group of recruitment or

Table 21

Amount of adaptation, expressed in dB in the four recruitment groups. All audiogram types and all frequencies included. Results expressed in absolute figures and as percentages. Adaptation of type III is given separately in second last column.

	0	5	10	15	20	25	30	35	40	45	≥50	III	total
Overrecruitment	1	10	6	6	4	3	3		1			1	35
	2.8	28.6	17.2	17.2	11.4	8.6	8.6		2.8			2.8	
Complete recruitment	18	58	64	90	61	30	21	7	3	6	2	26	386
	4.7	15.0	16.6	23.3	15.8	7.7	5.4	1.8	0.8	1.6	0.6	6.7	
Incomplete recruitment	19	54	70	88	61	53	29	15	2	4	2	69	466
	4.1	11.6	15.0	18.9	13.1	11.4	6.2	3.2	0.4	0.9	0.4	14.8	
No recruitment	5	9	16	15	9	7	4	3	1	2		5	76
	6.6	11.9	21.0	19.7	11.9	9.2	5.3	3.9	1.3	2.6		6.6	

Table 2

Diplacusi in various groups of adaptation and re ruitment (total/d placusis)

Recruitment	Adaptation I	II	III
Overrecruitment	4/1	8/?	5/2
Complete recruitment	80/36	89/40	56/25
Incomplete recruitment	97/30	91/36	75/34
No recruitment	?4/5	8/4	3/2

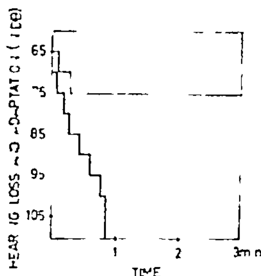


Fig 8 Role of diplacusis in evaluation of the r sult of adaptation test Adaptation at 6000 cps in 39-yea old ma te se geant Pu e tone audiog am divided dip Threshold tone decay measured from a sou nd" 10 dB/3 min = normal However when te ted from a ringing tone adaptation i definitel patholog cal ove 40 dB So en en type III

adaptation can be demonstrated by stati tical means Diplacusis is present in AT of all different grades of severity though it is true that it is slightly commoner in more severe injuries

Poststimulatory fatigue

The incidence of poststimulatory fatigue depends in large measure upon the accuracy of thre hold determination for pure tones In this study fatigue was found in the case of all audiogram types and each frequency (I II III) in an average of 33.2 per cent The time taken until the prestimulatory threshold was restored exceeded one minute in 12 9 per cent No significant differ ences were found when comparing the different audiogram types or frequencies. A typical bounce occurred only in a total of ten subjects

Table 23

Duration of fatigue as a function of hearing loss

		Fatigue = 15"	
Threshold	<30 dB	112	24.2
	30—60 dB	240	51.6
	>60 dB	112	24.2 %
		Fatigue = 30"	
Threshold	<30 dB	23	21.3
	30—60 dB	57	52.8 %
	>60 dB	28	25.9 %
		Fatigue>30"	
Threshold	<30 dB	35	25.2
	30—60 dB	70	50.4
	>60 dB	34	24.4 %

Table 24

Threshold of hearing in relation to duration of fatigue.

		Threshold <30 dB	
Duration of fatigue	>30"	35	20.6 %
	30"	23	13.5 %
	≤15	112	65.9 %
		Threshold 30—60 dB	
Duration of fatigue	>30"	70	19.1 %
	30"	57	15.5
	≤15"	240	65.4 %
		Threshold >60 dB	
Duration of fatigue	>30"	34	19.5 %
	30"	28	16.1
	≤15"	112	64.4 %

Looked at from the statistical point, fatigue is not connected with any of the recruitment groups. However fatigue appears to be significantly related to the amount of adaptation. The greater the adaptation, the more likely is fatigue to occur On the other hand it must be taken into account that a rapid and excessive adaptation makes it difficult to determine accurately the pre stimulatory threshold. Study of the relationship of the duration of post stimulatory fatigue to the amount of hearing loss did not disclose differences between the various groups of threshold values (Table 23 and 24) The values were only calculated for frequencies I and II it is customary to confine exposure tests to the low and medium range Frequency III comparatively

often coincides with 8 000 cp which I omitted in testing noise-sensitive subject

Speech audiometry

The speech unit of the audiometer was calibrated in such a way that the level of the pure tone threshold in the speech range coincided with that of the speech threshold. Table 5 shows the speech thresholds recorded in acoustic traumata of varying degree. In AT of grade I and II the speech threshold was almost invariably normal and even in grade III 78 per cent had a normal speech threshold. It must also be remembered that in speech audiometry no age corrections were applied in the absence of control material. Speech discrimination remains good in AT even in advanced cases (Table 6). The most frequent error was confusion of m and v (word pair malta valta). This accounted for 23 per cent of all errors. Spectrographic analysis of the formant structure of these consonant sounds in the test words concerned showed that a confusion of these letters is highly probable when account is taken of the average change in hearing caused by AT. In addition these two words (malta valta) are meaningful and occur daily in Finnish conversation. The next commonest error was omission or addition of the Finnish plural ending t (13.5 per cent). As an example the words wrongly repeated by a 44-year old senior sergeant (audiogram in Fig. 9) are given below each followed by the correct equivalent at right

Table 5

Speech thresholds in AT of varying degrees

Speech threshold	Grades of severity I	II	III	IV
10 dB	42	94	146	3
11—20	1	5	40	8
21—30			1	5
Over 30				9
Total	43	99	187	25

Table 6

Speech discrimination in AT of varying degrees

Discrimination ability (%)	Grades of severity I	II	III	IV
100—90	43	98	173	16
89—80		1	10	4
75			4	1
70				2
50				1
15				1

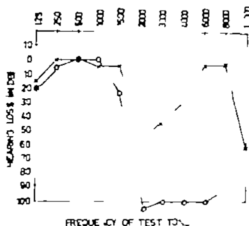


Fig. 9 Audiogram of 44-year old senior sergeant The words wrongly repeated in the speech audiometric test are given in the text and they may be regarded as typical for the entire series.

left ear	löysin	[lɔysin]	öisin	[ɔisin]
	malta	[mʌltʌ]	valta	[vʌltʌ]
right ear	kiiski	[ki ski]	vyyhti	[vy·hti]
	siniset	[siniset]	syiset	[syiset]
	veli	[veli]	möly	[mɔly]
	martti	[mʌrt i]	marssi	[mʌrs i]
	matkaa	[mʌtk.a]	maksaa	[mʌksa]
	leira	[leirʌ]	nöyrä	[nɔyræ]
	hylkeen	[hylke n]	syököön	[syɔkɔ n]

Apart from the word "leira" all the misinterpreted words are meaningful and occur in everyday conversation.

4 SPECIAL CASES

Case 1 E. K., Senior Sergeant 38 years of age

During training practice to accustom soldiers to explosions a 75 kilogram trinitrotoluene charge exploded at a distance of 20 metres. The subject was "completely deaf" for a day and this was followed by ringing in the ears for two weeks. Hearing has been poor since (Audiogram Fig. 10). He complains of constant tinnitus aggravated on the slightest exertion. The hearing tests in fact were made in three stages. They had to be interrupted because tinnitus increased to the extent that the subject could not differentiate the test tone from the ringing in his own ear. During shooting camps his ears were always totally blocked following the first round of firing.

often coincides with 8000 cps which is omitted in testing noise-sensitive subjects.

Speech audiometry

The speech unit of the audiometer was calibrated in such a way that the level of the pure tone threshold in the speech range coincided with that of the speech threshold. Table 25 shows the speech thresholds recorded in acoustic traumata of varying degree. In AT of grade I and II the speech threshold was almost invariably normal and even in grade III 78 per cent had a normal speech threshold. It must also be remembered that in speech audiometry no age corrections were applied in the absence of control material. Speech discrimination remains good in AT even in advanced cases (Table 26). The most frequent error was confusion of m and v (word pair malta-valta). This accounted for 23 per cent of all errors. Spectrographic analysis of the formant structure of these consonant sounds in the test words concerned showed that a confusion of these letters is highly probable when account is taken of the average change in hearing caused by AT. In addition these two words (malta, valta) are meaningful and occur daily in Finnish conversation. The next commonest error was omission or addition of the Finnish plural ending *t* (13.5 per cent). As an example the words wrongly repeated by a 44-year old senior sergeant (audiogram in Fig. 9) are given below, each followed by the correct equivalent at right.

Table 25

Speech threshold in AT of varying degrees

Speech threshold	Grades of severity I	II	III	IV
10 dB	42	91	146	3
11—20	1	5	40	8
21—30			1	5
Over 30				9
Total	43	96	187	25

Table 26

Speech discrimination in AT of varying degrees.

Discrimination ability (%)	Grades of severity I	II	III	IV
100—90	41	94	173	16
89—80		1	10	4
75			4	1
70				2
50				1
15				1

Fig. 12.

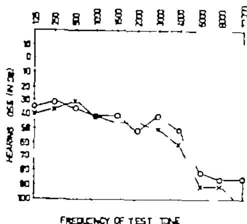


Fig. 13

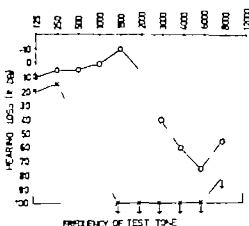


Fig. 12. Audiogram of 41 year old sergeant 1st class. Case 3 A shell bu st 5—6 metres from him during the war Hearing poor since. See text

Fig. 13 Audiogram of 48-year old captain. Case 4 During the war a bomb exploded on the other side of a stone against which he was holding his left ear See text

Case 4 Captain A. L. 48 years

During the war a bomb burst on the other side of a stone against which be was holding his left ear This was followed by continuous ringing in the left ear Hearing may have deteriorated at the same time, or perhaps later there was no time to attach greater significance to this under the circumstances. — There was incomplete recruitment (Fowler test) in the left ear at 500 and 1 000 cps overrecruitment in the right ear at frequencies I II and III Adaptation was in accordance with type I (Sørensen) in each ear Speech discrimination score 17.5 per cent in left ear 100 per cent in right ear (Audiogram, Fig. 13)

Case 5 Captain V V 54 years

A shell exploded 4 metres away from him during the war He had been "half deafened in the right ear maybe ever since. (Audiogram, Fig. 14) There was no recruitment in the right ear (Fowler test) Adaptation of Sørensen s type I Speech discrimination 96.7 per cent in right ear

Case 6 J K. Master Sergeant 49 years

He was exposed to several shell bursts at close range during the war and could then be "half deafened for weeks. He could not say when his hearing loss became permanent. In the right ear recruitment was incomplete at 1 000

Fig 14

Fig 15

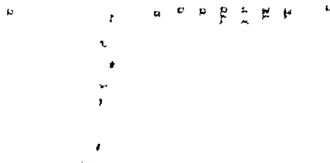


Fig 14 Audiogram of 54 year old capt in Case 5 A shell burst 4 metres away during the war See text

Fig 15 Audiogram of 42 year old master sergeant Case 6 Several shell explosions nearby in war time See text

cps and there was overrecruitment at 2000 cps Adaptation of Sorensen's type II The ability to discriminate speech was surprisingly good in the right ear 90 per cent The left ear was eliminated with white noise masking (at 70 dB effective level) using conventional and insert type earphones (Audiogram Fig 15)

Case 7 O S Sergeant 1 t class 49 years

In 1940 during the war a shell burst at a distance of 2 metres and his right ear became deaf It is possible that a rupture of the tympanic membrane was sustained at the time It healed spontaneously as did hearing also after half a year On examination the eardrum was covered by a fairly large secondary membrane and there were distinct changes pointing to adhesive otitis. There was no recruitment in the right ear Adaptation of Sorensen's type I Speech discrimination score 100 per cent (Audiogram Fig 16) This is the only case in the whole series in which rupture of the eardrum from a shock wave can be suspected

Case 8 Captain A L., 35 years

Hearing was not objectively impaired (Audiogram Fig 17) There was incomplete recruitment Rapid and excessive adaptation pathological also at the frequencies where auditory threshold was normal (Fig 17) When adaptation was tested solely by means of ringing tones the rate was far more rapid still and pathological even at 1000 cps. Speech discrimination score 100 per cent Neurologic examination revealed no findings of special importance

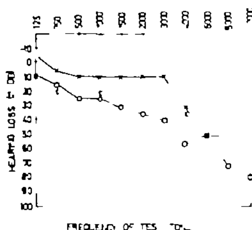


Fig. 16. Audiogram of 49-year old sergeant 1st class Case 7 A shell burst 2 metres from him, evidently resulting in rupture of the eardrum which healed spontaneously after half a year Hearing improved to its present level. See text

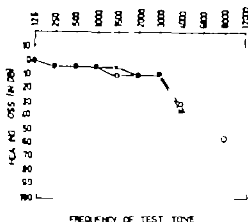


Fig. 17 Audiogram of 35-year old captain. Case 8. There is no subjective hearing loss. In spite of slight loss adaptation is of great amount and is pathological also at the frequencies with normal threshold. When adaptation is tested from a ringing tone (cf Fig. 8) it is still pathological at 1000 cps. Ability to discriminate speech 100 per cent

Case 9 Captain V K 38 years

Hearing had gradually deteriorated in the course of year. Hearing loss of dip type with incomplete recruitment. In this case too there was a pathologically large amount of adaptation at all frequencies involved in the dip (Sorensen's type III). Hearing for low tones was normal. In the adaptation tests the ringing tone only lasted a few seconds and then changed into a buzzing sound. For example at 1000 cycle (threshold — 5 dB) the amount of adapatation measured from a ringing tone was 70 dB measured from a "sound 70 dB. This finding was almost symmetrical on the left and the right side. Neurological examination showed nothing of special importance. Speech discrimination score 93.4 per cent

DISABILITY

Using Fowler and Sabine (1947) tables a hearing loss can be expressed as a percentage on the basis of the pure tone audiogram. The degree of disability can then be determined by dividing the result by two. Calculated on the basis of average audiograms (Table 14) the functional capacity of the ear is fairly slightly damaged (Table 27). In single cases the percentage loss can become considerably greater, for instance in the dip-type audiogram in Figure 2 the loss is 55 per cent and the handicap according to Fowler Sabine 27 per cent. Taking speech threshold as a rough index of the loudness of speech and whisper, it appears that only in grade IV (Table 25) did this threshold drop *to a level representing a compensable handicap (10 per cent). If both ears* are included the disability from AT may be estimated to reach 10—40 per cent in as few as 5 per cent of the subjects (10/197). When results are compared with the values in the Fowler Sabine tables it is found that only six of these ten subjects would be eligible for compensation. On the other hand there are several cases like the one shown in Figure 2 in which in spite of a normal

Table 27

Per cent hearing loss and disability calculated according to Fowler—Sabine tables. The mean values for Q_1, Q_2 and Q_3 are from Table 14, the average values (for both ears) from Table 15. Results expressed as percentages

	Per cent hearing loss		Disability	
	Left	Right	Left	Right
Q_3	0	0.3	0	0
Q_2	5.4	6.1	2.7	3.0
Q_1	26.2	28.3	13.1	14.2
ave	7.0		3.5	

speech threshold the disability calculated from the pure tone audiogram would be 20—30 per cent

The degree of disability can also be estimated from pure tone audiograms using the tables prepared by the Subcommittee on Noise Research Center (Lierle 1959) Each decibel by which the + 15 dB level is exceeded in the speech range (500 1000 and 2000 cps) produces a disability of 1.5 per cent. Using the speech threshold as the mean value for the speech range the disability can be obtained without difficulty from Table 25 The present series of AT included 10 subjects who thus calculated had a disability exceeding 10 per cent The maximum 50 per cent occurred in case 1

Using speech audiometry the Social Adequacy Index (=SAI) can be determined as a function of speech threshold and discrimination ability (Davis 1948) Though the table was originally prepared for PB words it seems that it can be used, without significant errors arising, for evaluation of speech audiometric results with words of trochee type. Davis has defined the normal limit of SAI as 94 (e.g. speech threshold 8 dB discrimination ability 100 per cent) The threshold of social adequacy corresponds to a SAI of 33 (e.g. speech threshold 33 dB discrimination loss 30 per cent) The limit of a compensable hearing handicap would equal a SAI of approximately 75—80 In the present study speech audiometry showed the hearing in 22 ears to be below this limit. Table 28 gives the SAI values analysed per ear studied and by degree of severity Socially inadequate hearing was present in 4 years (Case 1 SAI for left ear 26 for right ear 16 Case 2 right ear 29· Case 4 left ear 0 right ear 99) This method too gives results differing from those obtained from the Fowler—Sabine tables In the dip-type audiogram presented in Figure 2 the functional capacity of the ear would be reduced by 55 per cent according to Fowler—Sabine. The SAI however is 90 Rated by Lierle s scale the hearing handicap in this case would be 22.5 per cent.

Grade IV excepted, AT affects the ability to discriminate speech to a fairly slight extent Twelve out of 25 cases of grade IV were due to an explosion or some similar factor and thus were cases of acute AT Further every second acute acoustic trauma led to a hearing loss of grade IV In the group of

Table 28

Social Adequacy Index as a function of grade of severity of AT calculated for each ear

SAI	Grades of severity I		II		III		IV	
≥94	33	76.7	55	55.5 %	56	30 %	0	0 %
93—76	10	23.3 %	44	44.5 %	127	67.9 %	12	48 %
75—33					4	2.1 %	9	36 %
32— 0							4	16 %

chronic AT a IV grade hearing loss developed in only 7 of 183 cases. So it is seen that chronic AT does relatively seldom cause a compensable handicap.

Looked at from the angle of past history, it is found that a great number of the subjects with AT themselves considered their hearing normal (Table 7). Several felt that constant tinnitus was the most troublesome effect of AT.

4. GUN REPORTS

The most important physical characteristics of reports, as far as the etiology of AT is concerned, are 1) intensity, 2) spectrum and 3) duration. Great difficulties are encountered in determining each of these three characteristics, and this is due to the fact that sound pressure in a report reaches its maximum extremely rapidly and remains at this high point for a very short time, to fall again rapidly. Evaluation is also rendered difficult by a great number of reflections from the ground, weapon or objects in the environment, etc.

The intensity of reports was measured with an electric KISTLER pressure gauge. Table 29 shows pressure values, converted into decibels, for reports from the most commonly used weapons. The measurements were recorded at the firer's head position where the pressure generally is not maximal. The values are means calculated for several reports.

Spectrographic analyses of reports from four commonly used weapons are presented in Figures 18, 19, 20 and 21. These figures have three parts. Below is seen the basic sonagram, from which the point to be more closely analysed for the various frequencies is chosen and which also permits evaluation of the duration of reports. An intensity curve indicating the relative distribution of sound energy as a function of time is seen passing across the basic sonagram. The duration of a report can easily be determined from this curve. Above are shown the results of two or three frequency analyses. The Sonagraph has here analysed, with a narrow band filter, the relative amount of sound energy accumulated within 45 cps and 5 msec. (= 1 horizontal line). The sound of a report is delivered into the spectrograph in considerably attenuated form, and for this reason the result of analysis expresses the relative intensity. Knowing the absolute intensity of a report (Table 29), it is possible also to calculate the absolute intensities at the

Figs. 18—21. Spectrographic analyses of reports. In the lower half is seen the basic sonagram; the area selected from it for more detailed analysis as regards frequency spectrum is marked with the vertical line and numbered 1, 2, 3. The basic sonagram is traversed by an intensity curve indicating the relative distribution of sound energy as a function of time. The duration of a report can easily be determined from the curve. The upper half of the figure shows two or three results of frequency spectral analysis. With the aid of a narrow filter the spectrograph divides the relative amount of sound energy accumulated within 5 msec into 45 cps bands (= 1 horizontal line).

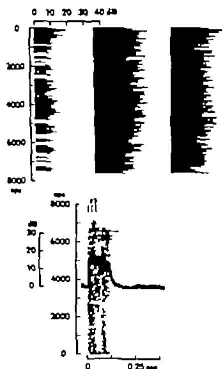


Fig. 18. Automatic rifle.

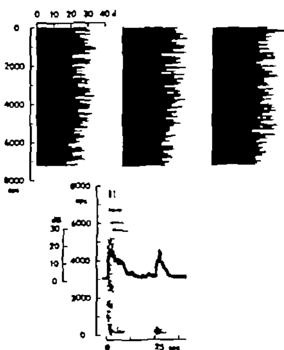


Fig. 19. Light mortar (80 mm)

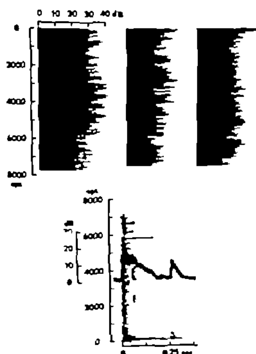


Fig. 20. Antiaircraft rifle VKT (20 mm)

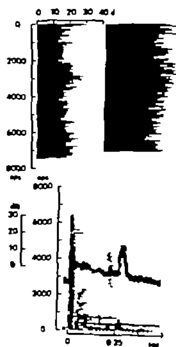


Fig. 21. Recoilless antitank gun (55 S 55)

Table 79

Intensity of report produced by different weapons.

Weapon	mmHg	dB
Pistol	37.5	165.0
Rifle	50.7	170.6
Automatic rifle	54.0	171.1
81 mm mortar	64.0	172.6
120 mm mortar	83.0	174.9
20 mm antiaircraft rifle	88.0	175.4
Recoilless antitank gun (55 S 55)	[illegible]	185.6
Field cannon 105 H/61—37	377	185.0

various frequencies The intensity curves show well how great a part the reflections play in the sound of reports Sound energy remains intensive up to relatively high frequencies and the physical maximum coincides mainly with the middle frequencies considered critical

Gun reports vary greatly in duration from 1 msec to 0.25 sec., depending above all upon technique of measurement and reflection If the duration of only the peak pressure is measured the values range from 1 to 3 msec according to the weapon used On the other hand the time taken for sound pressure to return to normal may be taken as the basis of measurement under field conditions the duration of reports then ranges from 0.1 to 0.25 sec If there are ample chances of reflection being present for instance when firing in a shooting gallery the duration of a report may be many times greater even several seconds.

V DISCUSSION

It has been customary to classify acoustic traumata by their cause into two groups, those referable to continuous or intermittent noise and, on the other hand, to sudden shock waves reports or explosive blasts. The greater part of previously published studies have been confined to the former group The functional quality of hearing loss due to AT has been the subject of only a few investigations based moreover on a fairly limited number of cases. In addition the methods of investigation used were often not acceptable for diagnostic purposes.

The present study was designed to elucidate the clinical picture of acoustic injury caused by gun noise or blasts — a subject still insufficiently known. For this purpose tests were selected that are practicable and suited for all available clinical audiometers require no additional equipment and are widely accepted by investigators These tests were assumed to provide adequate information on the functional characteristics of the ear and they would seem to be of value also in orientating determination of the anatomic locus of the injury

Following a preliminary screening test an audiologic survey was conducted on 197 regular army personnel with hearing loss indicative of AT in one or both ears. Auditory lesions other than AT occurred in 9.6 per cent. This percentage does not include losses due to presbycusis and sociocusis Taking into account also those nine subjects who had AT in one ear and a conductive hearing loss in the other the figure for losses other than AT rises to 11.5 per cent among regular personnel. This is slightly more than in Jusellus s (1962) study concerned it is true with a definitely younger age group subjects on an average 20 years old The total of regular personnel studied was 422 and of these 241 had AT In the majority of cases (93 4 per cent) the acoustic trauma was regarded as chronic. This being the case, the series appears to be fairly uniform.

On the basis of anamnestic data, it is not possible to diagnose AT at least not in the early stages owing to the presence of numerous classical symptoms of AT in normal hearing subjects also (Table 7) It arouses attention that hearing was often subjectively impaired in personnel with normal hearing.

In the Army AT is more common among field artillery personnel than in the oth branches of service (Table 4) This is probably explained by the fact that cr nscripts serving in the field artillery undergo fairly complete training in the use of small arms too and so the acoustic exposure of instructors is far greater than in other branches of service. The average incidence of AT (57 per cent) coincides well with, for instance Flodgren s (1945) results.

Pure tone audiograms vere divided, according to Hagermann s classification into three types. 1) dip 2) divided d p and 3) abrupt. In many cases

recruitment can change for the same reason into the reverse of recruitment (Dix and Hood 1953 Hood 1955) This source of error can be eliminated in large part in the monaural Reger test by utilizing a short stimulus Even grade I cases of AT however need not necessarily be associated with recruitment As shown by Beagley (1965 a) the anatomical findings may include separation of Hensen's and Deiter's cells which in its turn protects the hair cells from damaging sound stimulu As a result the hydrodynamic circumstances in the cochlea are changed the movements and at the same time sensitivity of the hair cells decrease very much (von Békésy 1960) a finding confirmed by electro-physiological study Thi might account for the absence of recruitment and of pathological adaptation in a few cases of AT with slight hearing loss

The cases with dip did not differ essentially from those with divided dip as regards the presence of recruitment at the various frequencies In the cases with audiograms of abrupt type however incomplete recruitment was clearly more frequent (Table 18) Because of the small number of subjects studied the statistical treatment of the material was unreliable in this respect At frequency I loudness recruitment was relatively least common the loss in hearing was also sometimes fairly slight at this frequency (Figs. 6 and 7) Taking account of Fletcher's and Munson's loudness curve the technical error can then in such cases be relatively greater when Reger's test i used so loudness recruitment becomes apparently less In addition to the above factors the hearing los may be ascribed in part to presbyacusis usually thought to be unaccompanied by recruitment (de Bruine-Altes 1946)

Loudness recruitment can be of prognostic significance (Harbert and Sataloff 1955) Recruitment seems to be mainly associated with progressive hearing loss To check this statement control studies at regular interval would be required In any case this study may be considered to lend indirect upport to the idea that recruitment has prognostic value

When an acou tic trauma has advanced to its definitive stage (grade III) recruitment often i either incomplete or absent It is evident that the damage has then extended to the inner hair cell which respond to stronger stimuli

The result of the present investigation are found to point in the sam direction a several previou tudies dealing with deafness induced by continuous noise (Da is *et al* 1950 Harbert and Sataloff 1955 T Palva 1957b Meyer zum Gottesberge 1954) Owing partly to the ize of the series partly to th old already permanent hearing losses incomplete or absent recruitment here account [illegible] greater proportion than in earlier studies Compared with [illegible] tudie on AT the occurrence of recruitment on the whole corr [illegible] previous findings

Electro-phy [illegible] the cochlea and auditory nerve (Gisselsson and Sorensen [illegible] audiologic studies (Reger and Kos 1952, Sorensen 19[illegible] 1962 etc) have demonstrated that perstimulatory ad[illegible] bably a sociated with retrocochlear

pathology i.e. with functional impairment of the acoustic nerve or the central auditory pathways Pathologic anatomical findings in AT indicate that the acoustic nerve is involved, though definitely later than the hair cells

The limit of normal adaptation was taken as 0—10 dB and values exceeding 30 dB and adaptation of type III were considered distinctly pathological (Sorensen 1962 Palva 1964) In the present study adaptation was found to increase highly significantly with an increase in severity of AT (Table 20) Adaptation was of slightly greater amount at the higher than the lower frequencies Average adaptation at frequency I was 13.58± 10.20 dB at frequency II 17.54 ± 9.30 dB and at frequency III 18.04 ± 8.85 dB There is no significant dependence between recruitment and adaptation (Table 21) though there is a definite trend. as adaptation increases loudness recruitment decreases. Adaptation of type III seems to be connected mainly with incomplete or absent recruitment Even though adaptation in the same ear is roughly similar at the different frequencies it may change from normal to pathological within one octave. In addition, pathological adaptation was found in all groups of recruitment as follows overrecruitment 5.6 per cent complete 11.5 per cent incomplete 19 7 per cent and no recruitment 14 4 per cent. Excessive adaptation during the first few seconds (relapse) when the auditory threshold may fall in an instant by 20—25 dB affects greatly the determination of not only the pure tone threshold but also of recruitment and always causes some degree of uncertainty in results. In these cases a sound stimulus shorter than usual must be applied in balance tests. For a satisfactory result to be achieved, recruitment must also be tested several times with the same sound pairs and at the same frequencies. The subjective sensation of loudness is oppositely affected by recruitment and by adaptation (Dix and Hood 1953) Recruitment is only demonstrated when the on-effect is essentially normal (Hallpike and Hood 1951) By reason of relapse the value obtained for pure tone threshold is often better than the true one Dandy (1934) etc., have reported that the pure tone threshold can remain normal in spite of a large portion of the auditory nerve being cut off. In addition as indicated by experience with, for instance, acoustic nerve tumours the ability to discriminate speech is much reduced in cases with pathological adaptation even although the pure tone audiogram may be normal. It is possible that the on-effect is the electro-physiological equivalent of relapse and therefore should be separated from perstimulatory adaptation proper (Hood 1950 van Dishoeck 1953) This is also suggested by Jerger's observation (1955) to the effect that when using continuous noise in adaptation tests and delivering simultaneously short signals at the same frequency and intensity the loudness of the continuous sound disappeared in some perceptively deafened subjects whereas the "pips remained audible. The short tone stimuli were capable of eliciting the on-effect although the continuous tone elicited no response in the hearing synthesis. In practice however it is impossible in audiologic tests to distinguish on-effect and perstimulatory adaptation from one another

Comparison of the present results with earlier ones i difficult because of differences in method used and material studied Dieroff (1957) used white noise of 80—90 dB inten its a timulu for 20 minutes and then recorded the threshold Adaptation" under the conditions includes a fatigue com ponent Later (1955) he used the threshold decay test in a fairly extensive series However a far a concern adaptation the results are presented in term of a kind of recruitment mea urement and it follows that the result can be con idered tendentious Yet acoustic trauma in Dieroff's tudy is not always a sociated with patholo-ical" adaptation He states "We saw unmistakable cases in which recruitment was definitely demon trable but the Threshold Tone Decay Test did not point to a vulnerable inner ear since no patho-logical adaptation was found" He calls attention further to the wide dispersion of adaptation values. Recently Dieroff and Kowalik (1965) reported on an exten ive series (338 ubject with AT) A in the above tudy "recruitment" was tested with the Langenbeck noise audiometer The study wa based on severe cases and a typical C_5 dip only occurred in a few since it i only seldom that subject with acoustic traumata of uch slight degree are referred for examination" Contrary to hi earlier views Dieroff here doubts whether the adaptation test can be used at all for tudyin cochlear pathology While in lighter injuries there i u ually no pathological adaptation it increases greatly with severity of the trauma In the opinion of Pestalozza and Cioce (1962) adaptation i generally within normal limits or only slightly increased in early cases of AT wherea adaptation values can be highly abnormal in severe cases "The amount of adaptation i more directly related to the degree of hearing los than to the amount of recruitment The findings in the present study upport the views of Pestalozza and Cioce and of Dieroff and Kowalik and in disagreement with Dieroff s earlier report confirm that the adaptation test cannot be used in determining recruitment This i graphically represented in Figure 22 based on analysi at nearly 1000 frequencies

The interpretation of adaptation i influenced in large measure by dipla cu is. In many cases a steady ringing tone changes ubjectively and i ex perienced as an undulating tone varying in pitch and/or inten ity "like the buzzing of a mosquito In other ubjects the sensation of a ringing tone pa ses quickly but they continue to hear a humming buzzing or soughing sound The same phenomenon has been described by Pestalozza and Cioce (1962) and others It i often impos ible for the ubject under tudy to decide when the tone hanges in quality a ringing tone and humming may be present coincidentally and the ringing tone may change from high to low pitch If the loudnes of pure tones alone were to be recorded in testing adaptation thi would make the result extremely uncertain. On the ba is of electro-physiologi al tudies of the cochlea and auditory nerve the hair cells have no adaptation proper CM i directly related to grow th of intensity The action potential f the auditory nerve i characterized by adaptation From electro-phy iologi al tudies diplacu is does not seem to be associated

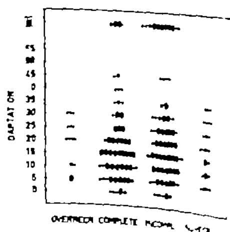


Fig. 22. Adaptation in different types of recruitment. Amount of ... as dB for types I and II. In addition, type III is presented ... circle = 10 observations, medium size circle = observations ... Large ... observation. There is no correlation between adaptation and ... one

with damage to the auditory nerve since the nerve fibres f... the rule of all or nothing. The anatomic site of diplacusis rests ... on the ...ations. This phenomenon might be related to damaged ha... partly capable of functioning but affected by functional fatigue. The ... response of the basilar membrane to a tone stimulus might be an add... al factor. A continuous stimulus affects the hair cells of several fre... causing a change in subjective quality of the tone as the ... to the stimulus loses functional power. Factors with ... specific possibly changed hydrodynamic circumstances in ... are also the the inner ear. It seems very likely that the locus of d... disturbances in peripheral to the auditory nerve. Assuming that the ... in structures the function of that nerve the essential point ... test indicates the way in which the impulse set up by the stim... of sound but fibres. On the above grounds the testing of adapta... along the nerve on the hearing of sound. The importance of ... study is based from Table 2... and Figure 8. Statistically diplacusis ... clearly apparent to any one group of recruitment or adaptation ... to be related ference between the various groups of ... a distinct dif... diplacusis. Using a self-recording audiometer ... the presence of ... tation, it seems possible to eliminate diplacusis ... 1947) to test adap... ...ing ing tone becomes a soughing sound and, if the ... adaptation the ... ...able tarily the ringing tone reappears. This can ... interrupted "moment ... is ex... However when thus interrupting the test tone ... many times over ... difficult definitely pathological to normal — a phen... may change ... ...ee can when special tests for this purpose were ma... ...rved in this ... com... it is important not to interrupt the stimulus ... ...sen's opinion ... seri... about a fresh on-effect because of the shor... ... this alwa... ...ite period

The "special cases" described above include two (Cases 8 and 9) with strongly pathological adaptation also at frequencies where threshold was normal. Similar cases have been presented by Carhart (1957) and Dieroff (1958). In Dieroff's case one ear had been damaged by explosive blast, the other ear was normal. In this normal ear adaptation was pathological at the frequencies corresponding to the dip in the other ear.

The clinical importance of poststimulatory fatigue is still not definitely known. It is possible that those parts of the inner ear that fatigue during experimental or occupational noise exposure are exactly the same elements as are destroyed after years of such exposure (Theilgaard 1951). Electrophysiological researches (Gisselsson and Sorensen 1959) have indicated that fatigue does not appear in CM potential until stimulation reaches high intensities (>95 dB). The pathologic anatomical changes described, i.e. splitting of the Hensen-Deiter's cells (Beagley 1965 a) and swelling of the nuclei of the outer hair cells (Wüstenfeld 1957), also appear only in response to intense sound stimulation. TTS is not associated with any demonstrable ultrastructural change (Beagley 1965 b). It was found recently (Faltynek and Vesely 1964), however, that experimental animals treated with adenosinetriphosphate injections showed considerably less fatigue. The disturbance accordingly might be located in the energy producing system. This is consistent with present-day theories on the origin of AT.

The determination of fatigue carries many possibilities of error. First and foremost, the presence of fatigue depends upon the accuracy of pure tone threshold determination, as well as on the amount of adaptation. Obviously it is for these reasons that the occurrence of fatigue increases significantly with the amount of adaptation and particularly if adaptation is initially rapid. Ward (1967) compared the different tests designed to separate out noise susceptibles and found that the rate of adaptation, rather than its absolute value, might conceivably be a good index of susceptibility.

Poststimulatory fatigue is not related to the grade of severity or the stage of AT (Table 23). This seems to mean that cell destruction is gradual, the damaged cells are destroyed little by little, the damage extending to new cell groups. A great amount of fatigue seems to indicate that a hearing loss has not as yet reached its definitive level, the process is continuing, in other words the damage in the area responding to sound at the point being tested is still incomplete. So it seems that the main clinical importance of the fatigue test is in evaluating the prognosis of the hearing loss. Considering that, when testing various frequencies within one octave, fatigue may or may not be present though the sound stimulus is kept unchanged, this study also favours that view that the test cannot be employed for separation of noise susceptible individuals.

The results of speech audiometric tests may be considered surprisingly good in cases of AT, even for advanced ones (Case 6 and Table 26). It should be borne in mind that the conditions of test were ideal, there was no disturbing environmental noise. The results correlate well with those obtained

using filtered speech (low-pass filter) (cf A. Palva 1965) Elimination of high tones affects discrimination of consonants to a much greater extent than vowels (Fletcher 1929) — a fact noted in the present study also. True in the case of individual sounds notably consonants their correct under standing often depends decisively on the preceding or following sound (Fry 1964) The majority of the speech audiometric mistakes seem to be accounted for on this basis In most cases the words wrongly repeated were also meaningful and in daily use. From the speech threshold values it seems obvious that the "classical tests by speech and whisper are not of diagnostic value in cases of AT at least not in its early stages.

The case of a 48-year old senior sergeant wounded by a pistol shot (Case 2) is of special interest He had a severe hearing loss of dip type with incomplete recruitment and excessive adaptation (Sørensen s type III) also at 1000 cycles. The ability to discriminate speech was very poor The audiologic findings also accorded well with acoustic nerve tumour Neurological examination was negative.

A consideration of the various methods of rating disability on the basis of pure tone or speech audiogram led to the conclusion that, on an average, the disabling effect of AT is fairly slight. This is supported by the anamnestic data. In AT the methods available for such evaluations correlate poorly almost opposite results may be obtained in many cases by various methods of calculation. The most important purpose of the function of the ear and hearing is the understanding of speech in daily life. Consequently speech hearing tests of different kinds seem to provide the most natural basis in rating disability A loss of pure tone thresholds alone without limitation of hearing for speech or whisper does not legally speaking, represent a compensable handicap (Lehnhardt 1965) Judging from the results of this study the handicap from AT can best be evaluated by means of the Social Adequacy Index, based on speech audiometry and by the table prepared by the Subcommittee on Noise Research Center based on pure tone audiometry From these it was found that a compensable disability (≧ 10 per cent) due to AT had developed in about 5 per cent of the series and in about 3 per cent of the total regular personnel. This figure must be considered low Allowing for the fact that intense tinnitus can further increase the handicap by some 10 per cent (Boenninghaus and Wittgens 1962) the number of those entitled to compensation increases many times over It is impossible to state a precise figure the extent to which tinnitus is disturbing depends so essentially on individual factors. Generally speaking, hearing losses from acute acoustic trauma, blast or the like are more severe and affect the hearing for speech and whisper in chronic AT however a severe, compensable hearing loss develops comparatively seldom perhaps only if there is exceptional sensitivity As a whole the rating of disability from AT is difficult One attendant problem is whether the hearing loss accompanying age can be included or whether it should be deducted prior to defining the compensation The use of average tables cannot be defended even in this series

there were several ubjects over 50 years of age whose pure tone threshold at 12 000 cps wa still on the better side of + 10 dB Another problem is posed by the circumstances in which the hearing tests are usually carried out Artificial situation are created in whi h the result are affected by environmental noise to the lea t possibl extent From the point of view of determining the degree of di ability this must be con idered unfavourable the loss of earning capacity hows itself in daily life and at the work place indeed not under ideal condition In the peech test especially provi ion should alwa be made for background noise in consideratio n of the dif ficulties that an AT patient may experience in everyday life Thi principle is applied for instance in audiometric test with filtered peech (P llack 1948)

Some important clinical characteri tic of AT are presented in Table 30 It hows that a cautiou position mu t be taken in regard to the various diagnostic criteria. However AT ha also typi al features which are related especially to the grade of severity of the lesion and its duration In early acou tic injury still in proces of developing i characterized by a dip complete recruitment and normal or nearly normal adaptation In farther advanced cases loudnes recruitment decreases and adaptation increases The ability to discriminate peech and the threshold for peech remain good

Table 30

Summary of some important characteri tics of AT

Series	normal hearing	33.2	Type of audio ram	dip	75.5 *
	AT	57.2 *		divided dip	10.7
	other lesion of ear	9.6		abrupt	13.8
	(total 422)			(total 355)	
Recruitment	overrecruitment	3.6	Adaptation	normal	34._
	complete recruitment	40.1 *		patho logical	15.4
	incomplete recruitment	48.4 *		as rape	16._ dB
	no recruitment	7.9		diplacu i	40.2
	(total 963)			(total 963)	
Speech threshold	<10 dB	80.5 *	Speech discrimination	>90	93.4
	11—20	15.3 *		90—80	4.3
	21—30	1.7		<80	2.3 *
	>30	2.5		(total 355)	
	(total 355)				
Social Adequacy Index	94	40.7			
	93—76	54.5			
	75—33	3.7 *			
	[illegible]	[illegible]			

in far advanced types of loss too Fairly rarely does an acoustic injury become severe enough to represent a compensable hearing loss If so it is usually a question of acute AT due to *explosive blast or something similar*

Comparison of the thus-obtained audiologic picture of AT due to gun noise with noise induced hearing loss shows some small differences. In detonation trauma the dip is frequently deep and steep (cf Fig. 2) In *ordinary noise trauma* the permanent dips are also more pointed and narrower and consequently somewhat more slender than the temporary dips (Gravendeel and Plomp 1961) In the detonation injuries here included the maximum dip also clearly affected higher frequencies (e.g 3 500 cps) than presupposed by the classical C_5 dip concept It is true that according to van Dishoeck and van Gool (1951) and Gravendeel and Plomp (1961) the maximum dip is at frequencies above 5 000 cps also in permanent hearing losses from continuous noise whereas in temporary lesions it is at about 4 600 cps. In view of this fact it is possible that, in several studies on AT a sufficiently long respite period has not elapsed prior to the testing of hearing. It should also be noted that there are a variety of etiological factors The greater the intensity of the traumatizing noise the higher are the frequencies affected by maximal TTS (Wegel and Lane 1924 Nakamura 1964) Lehnhardt (1965) writes that a permanent dip occurs around 6 000 cps if the damaging noise is very loud, but lower frequencies are affected by noise of weaker intensity The noise spectrum is also of major importance in this respect. In a great number of cases however it is impossible to make an etiologic" diagnosis from the type of dip (Ward and Glorig 1961) The physical differences between continuous noise and detonation are evened out in the case of noise from automatic weapons The reports caused by these are comparable to intermittent noise as already shown by Murray and Reid in 1946 No disparity was found when comparing cases of noise trauma with the present series of detonation injuries from the point of view of recruitment phenomenon (Boenninghaus *et al.* 1955 Palva 1957b) adaptation (Ward *et al.* 1961 Pestalozza and Cioce 1962) and speech audiometry (Glorig and Davis 1961 Lehnhardt 1965) The study of Ward Fleer and Glorig (1961) was designed to clarify whether auditory changes due to noise differed from those due to gun noise on the basis of clinical tests. In the authors opinion firing probably caused a steeper loss in hearing. As regards recruitment and adaptation there were no differences Ability to discriminate speech was good in both groups. These investigators consider that the term "noise trauma equals acoustic trauma They stress that no one has as yet shown distinct differences between the corresponding *histological results Accordingly it* seems preferable not to distinguish various forms of AT too sharply the more so as owing to mi ro-noise trauma (Gravendeel and Plomp 1960) and to sociocusis notably in old persons a large proportion of cases of AT can be regarded as in a way *mixed forms. On this basis it seems* that the *results here obtained* can be utilized in over-all diagnosis of AT regardless of the etiology in each case.

Studies of the physical properties of gun noise have indicated that the

sound pressure resulting from even a pistol shot exceeds the critical lim of 165 dB/0.003 sec (Plander 1965) The use of ear protectors howeve seems to prevent the development of AT on exposure to gun noise (cf Fig 1 It is possible that such protection is not sufficient in the case of explosiv blast for instance when sound pressures produced by heavy guns wer measured at the muzzle (not at firer s position as in Table 29) pressure exceeding 2 atm are obtained This probably equals the sound pressure c explosive blast

The frequency spectrum of reports calculated mathematically by usin Fourier s integrals differs definitely from the result of technical analysis. Th diagrams obtained in thi study by spectrographic analysis were compare with previous studies (Galloway *et al* 1955 Kryter and Garinther 1965) an the results found to be very much in the same direction It is evident tha each type of weapon has its own peculiar spectrum which is mainly relate to calibre amount of gunpowder and barrel properties From analyses o various weapons it seems that the smaller the calibre the higher are th frequencies where the physical maximum occurs Calculated by Fourier s integrals the physical maximum of the spectrum affects a relatively narrov band of the low frequency range In a technical analysis like the presen spectrographic one the medium and high frequencies are strongly represen ted As an evaluation of the average result it may be stated in agreemen with Lehnhardt (1965) that a report is a short "burst" of white noise

From the practical point of view the values for the duration of report are also of interest The duration of pressure maximum varies between 1 anc 3 msec But when a shot is fired in a shooting gallery and the total duratior of the report is measured it may be many times greater Firing of small arms is almost always done in groups in a shooting gallery As a result each firer s ears are exposed not only to reports from his own weapon but to those fired by others and to numerous reflexes from walls ceiling and from the hard floor Perlman (1941) thinks that a smooth solid wall reflects 96 per cent of the sound energy If the firers are at less than 8 ft distance from each other then each firer s ears are exposed to more danger from his neighbour s than his own weapon (Coles and Knight 1965) In this way the currently used practice of shooting seems actually aimed at creating favour able preconditions for the development of AT

VI SUMMARY

It was the purpose of this investigation to study the clinical audiologic picture of hearing losses caused by shooting among regular army personnel.

In an attempt to obtain a series as uniform as possible the military units to be studied were selected so as to exclude all possible causes of hearing loss other than gun noise. The total of regular personnel included was 422 and of these 241 (57.2 per cent) had AT Diagnosis was made by exclusion. Ear pathology other than AT was present in 9.6 per cent of the total series. In the majority (93 4 per cent) the acoustic injuries could be considered chronic only exceptionally was permanent hearing loss due to explosive blast or some similar cause. It appeared in the course of the investigation that AT cannot, at any rate not in the early stages be diagnosed by anamnestic means so frequently are the classical symptoms of AT found in normally hearing individuals while on the other hand, these classical symptoms may be absent in far advanced cases of AT

The methods used for audiologic analysis of AT were so chosen as to be suited for practically all the clinical audiometers available. Testing consisted of an ordinary pure tone audiogram, speech audiometry the monaural Reger test for recruitment the perstimulatory threshold tone decay test for adaptation, and determination of poststimulatory fatigue. The time was so chosen that, in each case, at least weeks or months had passed since the last occasion of shooting. Under these circumstances the AT if present must be permanent, and temporary threshold shift can be disregarded in evaluating the results.

The incidence of AT among regular army personnel of the Finnish Defence Forces was found to be fairly high. It varied from 43.2 to 68 7 per cent in the different branches of service being definitely higher in those branches with more acoustic exposure. Judged on the basis of average curves AT develops rapidly to its permanent level, possibly within five years. Cases of AT increase very highly significantly as a function of years of service and age. This has been interpreted in such a way that with continued exposure even initially resistant ears are gradually damaged, and the lesion then proceeds rapidly to its permanent level. When this level is attained the hearing is no longer markedly affected by similar acoustic exposure. Subsequent deterioration is due mainly to age-connected factors Fairly rarely does the hearing loss extend to the low tones this may occur as a result of explosions or in especially noise susceptible individuals. Hearing for speech therefore remains normal in most of the cases.

W th rare exceptions pure tone audiograms could be divided into three groups 1) dip (75.5 per cent) 2) divided dip (10 7 per cent) and 3) abrupt (13.8 per cent) Irrespective of audiogram type 9 1 per cent of the subjects

showed complete or incomplete recruitment at all frequencies tested I II and III (Fig 2) At the early stage of AT recruitment was complete in more advanced cases incomplete Statistically this ratio is very highly significant Perstimulatory adaptation was usually moderate at frequency I on an average 13.59 ± 10.20 dB at II 17.54 9.30 and at frequency III 18.04 ± 8.85 dB All frequencies included adaptation was of normal amount (10 dB) in 34.2 per cent With increased AT adaptation also increases highly significantly Definitely pathological adaptation (>30 dB or Sorensen s type III) was present in 15.4 per cent Pathological adaptation occurred in 5.6 per cent of the group with overrecruitment in 11.5 per cent of the cases with complete recruitment in 19.7 per cent of those with incomplete recruitment and in 14.4 per cent of the nonrecruiting cases. There was no statistically significant dependence between recruitment and the amount of adaptation Rapid adaptation of large amount caused great difficulty in determining recruitment Diplacusis was frequently (40.2 per cent) noted during adaptation tests. Viewed statistically diplacusis does not accompany any particular type of adaptation or recruitment It increases to some extent with an increase in AT Unless specially considered diplacusis may represent a great source of error in testing adaptation Poststimulatory fatigue was found relatively often if a precise pure tone threshold was aimed at This phenomenon seems illustrative of the prognosis for threshold at each frequency studied and it cannot be con idered associated with any particular types of trauma with the function of recruitment or with adaptation type Results of speech audiometry showed that both speech threshold and speech discriminating ability remain at a surprisingly good level even in advanced acoustic injuries.

The pure tone audiogram speech audiometry and the other tests mentioned above convey a fairly consistent idea of AT and so they can be recommended as a basis of diagnosis There are exceptions however for in tance Case 2 (p 54) — which audiologically bears great resemblance to acoustic nerve tumours

Morphologically the changes in AT affected in the main the outer hair cells of the cochlea and it is possible that degenerative lesions of the acoustic nerve are secondary phenomena. If complete recruitment indicates pure hair cell damage and pathological adaptation indicates considerable reduction of the number of active fibres of the auditory nerve then it may be assumed that only in a small proportion of the cases can AT be anatomically located by audiologic tests (Fig ?2) In a large proportion in any case the anatomic locus would be uncertain — merely hypothetical — in spite of the fact that in these cases too the pure tone audiogram shows a dip of entirely ordinary appearance A cautious attitude must thus be taken to the question of locating the lesions anatomically by means of audiologic tests Such tests may at the most be indicative of a trend

On the basis of various methods of rating disability — based on pure tone or speech audiometry — AT on an average produces fairly slight handicaps. This is supported by th patients own opinions on their hearing loss A

compensable disability generally speaking, only develops in acute AT resulting from explosive blast or similar phenomena or in exceptionally noise susceptible subjects It may be concluded that in no more than 3—5 per cent of the subjects under study did the disability due to AT alone exceed the 10 per cent limit

Measured at the firer s position the sound pressures caused by all usual weapons even a pistol shot exceeds the damage risk level of 165 dB All regular army personnel at some stage of their service act as shooting instructors so each one of them has a history of possible predisposition to AT Sound pressures measured in this study varied from 168 to 188 dB Spectrographic analysis showed that the physical maximum coincided with the medium frequencies considered most critical, and the smaller the calibre the more distinct was this energy distribution These findings accord well with recent views on the physical characteristics of gun noise. The average acoustic traumata in the present study were compared with the physical characteristics of the reports and were found to be in agreement. It is generally accepted that with greatly increased intensity of sound pressure the maximal TTS and the possible resulting AT shift towards higher frequencies In the present study the maximum dip occurred on an average at 5 500 cps and not at 4 000 cps as is usually the case in noise trauma.

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S U P P L E M E N T U M 223

THE EMBRYOLOGICAL DEVELOPMENT OF THE LIMBUS AND OF THE LATERAL AND ANTERIOR WALL OF DUCTUS COCHLEARIS IN THE RABBIT

A. CIMINO and G GRISANTI

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From the Oto-Rhino-Laryngological Clinic University of Palermo, Italy
(Head. Prof E. Borghesan)

ACTA OTO LARYNGOLOGICA

SUPPLEMENTUM 223

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UPPSALA 1967

Th[illegible] paper h[illegible] been [illegible]warded the second prize
R[illegible] 1966 at th[illegible] [illegible]th Congress of
the Ind[illegible] S[illegible]ty of La[illegible]
O[illegible] and Rhinology [illegible] held from
september [illegible] to october 2 1966

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Dedicated to
Professor Dr Ettore Borghesan

Fleandt and Saxen (1936) on the contrary assess that the entire stria is epithelial in origin

Shambaugh (1907) in his researches on pig embryos, mainly in consideration of the behaviour of the basal membrane has established that the cellular layer below the superficial epithelium of the stria vascularis, arises partially from connective tissue and partially from epithelial tissue

Recently Weibel (1957) on the basis of studies on the newborn mouse has reached the conclusion that the stria vascularis is formed by a superficial epithelial layer and by a deeper connectival one

Striking differences are also to be found in literature as to the real connections between vessels and epithelium in the different developmental stages. Actually not all authors agree in admitting that during embryonal life protoplasmic extrusion may sink into the epithelium and envelop the underlying vessels

We wish to remind in this item that Borghesan (1963) asserts that the maturation of the stria vascularis is successive to the maturation of the spiral canalicular system this, in the same author opinion would support the hypothesis of a humoral function of the canalicular system during embryonal life

The development of the spiral prominence and of the outer spiral sulcus has been differently described

Since the very first observations attention was called upon the existence of a peculiar tendency of the epithelial lining cells of this area to displace towards the underlying connective tissue These are the cells that Iwata has called "cells with roots" (Wurzelzellen) and that have been variously interpreted from the functional standpoint Shambaugh (1909) believes them to be a secreting glandular epithelium Iwata (1925) has attributed to these cell a contractile function which has been confirmed by Held 1926)

Fleandt and Saxen (1937) ascribe to the epithelial cell of external sulcus spiralis and to those that are sunk in the connective the function of endolymph reabsorption Borghesan (1947) describes in the spiral ligament of adult rabbits a peculiar canalicular system to which belong the epithelial cells, originated from the lining cells of external spiral sulcus He confers to this system the function of directing, both towards the cochlear canal and toward the vascular system the plasma secreted by the villi of the spiral prominence thus a safety system would be provided to maintain a constant endolymphatic tension in the cochlear duct

In a recent embryologic study on the rabbit, Borghesan (1963) gives more detailed information on the functional value of these structures in relation to the embryonal development

Weibel (1957) has also described the development of the spiral prominence and of the external sulcus spiralis without giving any particular functional signification to the radicular cells which sink into the spiral ligament

Also Anggård (1965) describes the development of the "Wurzelzellen" emphasizing the correlations of these cells with the spiral prominence and with the stria vascularis, without expressing his opinion on their functional significance

From the standpoint of the normal morphology of the crista spiralis Hensen (1871) and Kölliker (1861) believed that the "teeth" described by Huschke in 1832 were formed by a substance which had an epithelial origin subsequently Böttcher (1859 1869) demonstrated its connectival nature and Wintwarter (1870) described the superficial layer as a sort of superficial mosaic. Such an aspect was later confirmed by Denis (1901) and Vernieuve (1905) Retzius (1884) asserted that the mosaic aspect was to be attributed to the more superficial part of the lining epithelium on the contrary Lavdowschy (1876) had denied the existence of correlations between superficial mosaic and epithelial lining cells, considering the first one as an endothelial plate Retzius s observation was supported afterwards by Held (1902 1908) and Van der Stricht N (1908)

This aspect has been described in its embryologic evolution by Van der Stricht O (1918)

This author considers four developmental stages the first stage is characterized by a pluri-stratified lining epithelium which lays upon a fenestrate basal membrane *under it an areolar embryonal tissue can be found.* A second stage during which the connective tissue penetrates among the epithelial lining cells and forms the rudiment of the connective embryonal "teeth" A third and fourth stage during which the connective tissue and the interdental cells undergo those modifications which will end when the final structure is achieved.

It is interesting to point out that Van der Stricht O has described several channels in the subepithelial connective tissue which are connected with the bottom and the walls of the interdental sulci while the epithelial cells that line the sulci lose their cellular bounds and form syncytial plates

Very little has been said in reference to the functional significance [illegible] these structures The crista spiralis has always been considered as [illegible] anatomical structure of connectival or periosteal support without [illegible] other well defined function

MATERIAL AND METHODS

The study has been carried out on a series of Burgundy [illegible]
The foetuses were not classified according to their length, [illegible] to the day of embryonal life they were drawn—that is [illegible] the 30th day Moreover newborn rabbits have been [illegible] th day after their birth

Fixation was performed in Flemming's fluid [illegible]

embryos were fixed as a whole in those aged from 16 to 21 days, only head and neck were examined as to the remaining ones, only the temporal bones were fixed

Decalcification the duration of which was in accordance to the embryo s age was obtained with hydrochloric acid celloidin was used for inclusion and the sections were collected in series

After their fixation in Flemming s fluid and before their inclusion the embryos were colored *in toto* by ferric haematoxylin

PERSONAL OBSERVATIONS

15-days Embryos

In the thick mesenchyme directly adjoining the rudiment of the cochlear duct we observe that a thinned area has appeared on the basal turn (Fig 1) Right in the inner edges of this area the mesenchyme cells, besides rarefying, change their shape from a roundish into a longer one moreover while the nucleus becomes oval the cellular body lengthens a bit at both ends and anastomosing with the adjoining elements forms a set of meshes, so that all the area acquires a reticular a pect which was described by Streeter Besides, some cellular elements after going through a fluidifying process due according to Bötcher to fatty metamorphosis dissolve Lacunae are thus formed some f the lacunae join together and larger spaces appear (Fig 2)

The cross section of the cochlear duct already in this stage shows a rough di tinction of the three walls (Fig. 3) an anterior wall (A) a lateral wall (L) and a basal wall (B) Especially in the middle part of the latter we easily observe a thickening of the epithelium on which the reticulate membrane can be clearly seen

On the contrary that part of lateral wall where the stria vascularis will later develop is clearly made of a single layer of cylindrical epithelial cells, separated from the mesenchyme below by a distinct basal membrane These epithelial cells, very tall are supplied with a finely granular cytoplasm and furthermore towards the cochlear lumen, with a sharp cuticular edge show oval or elongated nuclei The peculiar arrangement of these ones, placed alternately now in the lower part of the cell now in the middle gives to the epithelium a stratified aspect (Fig 4) The epithelial lining is clearly limited at the bottom by the underlying connective that through being very rich in cellular elements, presents a scarce number of blood vessels placed at some distance from the epithelium

That part of the lateral wall, which will give rise to the spiral prominence and to the outer spiral sulcus is made of a thick layer of lining cells that borders directly and without any sharp limit what will become the contour lamina that at this stage is not yet cartilaginous The layer of lining cells



F 1–4.

is made of a cloak of epithelial cells in a pluristratified arrangement, bordering the other cells of connective nature that are provided with a large often fusiform nucleus, and arranged without any apparent scheme There is no clear limit between these two kind of cells, and not rarely we observe some capillary vessels passing from zone to zone We wish to remark that the epithelial cells on the surface appear swollen and therefore lighter than those of the basal layer

On examining the posterior inner tract of the embryonal cochlear duct, from which the crista spiralis will originate we point out that even here there is no clear-cut limit between the epithelium and the mesenchyme below

The surface of the epithelial lining in this area, as well as in correspondence to where the spiral ligament starts from, is finely fringed (Fig. 3) The mesenchyme bordering on the epithelial lining shows several capillary vessels with very thin walls, generally empty and set in different directions. The lining epithelial cells (Fig 5) arranged in many layers, have large roundish nuclei. The chromatin is either disposed in more or

less thick lumps, or granular and is inclined to settle into regular columns. Their cytoplasms are thick in the basal strata but the nearer we go to the open surface the lighter they grow until they acquire a light almost swollen hydropical appearance. It is this peculiar aspect of the cytoplasm that at low magnification makes this zone look fringed. In the basal part on the contrary the epithelial lining borders on the mesenchyme very rich in nuclei many of which are morphologically similar to the epithelial ones. In it large empty spaces are found lined with cells of endothelial type (Fig. 6).

21 days Embryos

In this stage since the fluidifying process of the mesenchyme adjoining the basal turn goes on we find a cavity that we may now call scala vestibuli owing to its connection with the cochlear duct (Fig. 7). In its lumen though we still find several mesenchymal sprouts especially at the inner edges of the scala (Fig. 8) where they gather again to the contour of the cartilaginous capsule and the anterior wall of the cochlear duct.

This wall that till the 18th day is made of epithelial cells rather tall and quite similar to the others lining the rudiment of the cochlear duct appears now as formed by one layer of cubic cells, with a deeply coloured nucleus and finely granular cytoplasm (Fig. 9). This epithelium looks clearly separated by a distinct basal membrane from the stratum of mesenchymal cells gathering at the edges of the scala vestibuli. In this layer some capillary vessels are found which come from the thick area of crammed mesenchymal tissue adjoining the floor of cochlear duct: their course is parallel to the epithelium border (Fig. 9).

The first rudiment of Reissner's membrane then can be considered already established in its basic structural elements but its aspect is still far from resembling the ultimate look of Reissner's membrane.

The anterior wall is quite distinct from the lateral wall where for the first time we make clearly out the limit between the zone where later the stria vascularis will develop and the outer spiral sulcus zone marked by the higher epithelial layer (Fig. 8).

The epithelium lining the lateral wall of the future stria is distinctly separated by a basal membrane (Fig. 10) from the connective tissue below and is made of a mere line of cells somewhat shorter than in the former stage. These cells show an oval or roundish nucleus, deeply coloured and placed generally either in the middle of the cell body or in that part of the body facing the lumen of the cochlear duct. The epithelial lining we just described continues in the fore part with the cubic cells of Reissner's membrane and behind with the taller cells of sulcus spiralis.

The connective tissue between this epithelium and the cartilaginous capsule is now showing at its edges some thinning of the cellular elements: the capillary vessels are somewhat inclined to approach the lateral wall of

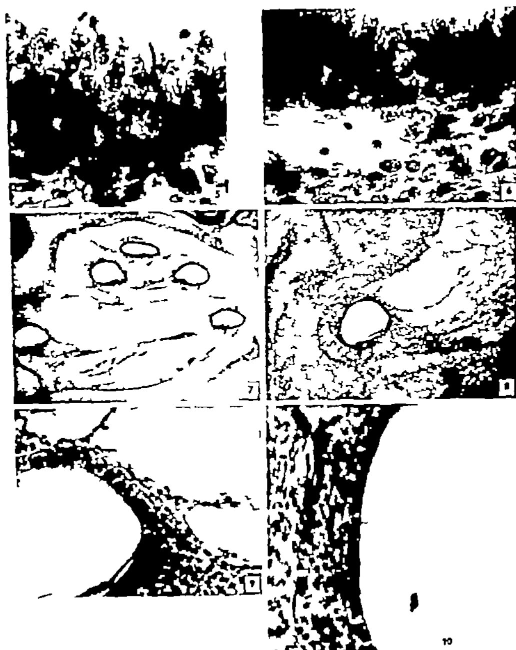


Fig 5–10.

the cochlear duct, especially near that part of the epithelium out of which the stria vascularis will later grow (Fig 10)

The connective below the epithelial tract corresponding to the spiral prominence and to the outer spiral sulcus is lacking in fibres but rich in cells, which are thicker towards the cartilaginous capsule and thinner all over the rest (Fig. 11) The ligament is provided of a rich vascular network

whose vessels run generally as a spiral (Fig 12) The lack of a sharp limit between the connective tissue of the ligament and the epithelial lining, that will originate the prominence and the outer spiral sulcus is evident enough Whereas this limit is clearly defined in the tract corresponding to the stria vascularis, it is worth noticing, too, right sideways the epithelial rims representing the outline of the Corti organ and on which the tectorial membrane spreads the difference between the cells of the outer spiral sulcus, with a homogeneous and dark cytoplasm, and those of the future spiral prominence among which some light spaces do appear (Fig 11)

The zone corresponding to the crista spiralis is clearly recognizable at this stage as it looks like a thickening of the mesenchymal tissue corresponding to the posterior median corner of the cochlear duct It is often crossed by capillary vessels of some size (Fig 12) At greater magnification we notice that the mesenchymal thickening imperceptibly changes into the epithelial cover (Fig 13) On its surface we can perfectly recognize the tectorial membrane adhering in its inner part whereas it seems to come off towards the large epithelial rim. In the most superficial layer of the epithelium we observe some lighter spaces alternated with darker furrow like ones, which probably are to be ascribed to intercellular spaces. The observation with immersion lens, of the mesenchymal tissue forming the body of the crista spiralis (Fig. 14) shows the presence among many cells, of a loose mesenchymal tissue of a rich network of more or less large capillary vessels, arranged in spirals or in wide bends anastomosing with the venous system of the spiral ganglion As these capillar vessels look generally empty (Fig 14) they probably contain plasma and are presumed to connect the basal zone of the epithelial layer of the crista spiralis with the venous vascular system of the spiral ganglion

25-days Embryos

At this stage of development we can observe a further thinning of the mesenchymal layer covering the vestibular face of Reissner's membrane even the epithelial layer looks lower and the whole membrane the mesenchymal sprouts having disappeared is by this time longer and somewhat lighter than in the former stages.

The part of lateral wall of the cochlear duct where the stria vascularis will originate appears to be made of one line of almost cubic epithelial cells, owing a lighter cytoplasm in the basal zone and a round nucleus of this one we point out both its dark colour and its position towards the cochlear lumen This epithelial layer is always definitely limited by a well defined basal membrane dividing it from the underlying connective of the spiral ligament (Fig 1) The latter shows a perceptible thinning of the compounding cellular elements in its external two-thirds, whereas the inner zone adjoining the epithelium is made up of a connective fascia very rich in roundish nuclei some of which deeply coloured some lighter













FIG. 11 16.

On the 25th day of embryonal life the spiral prominence begins to come clearly into view since it starts jutting out into the cochlear duct in the form of a cellular thickening containing a vascular tangle covered with a layer of epithelial cells There are no noteworthy changes in the outer spiral sulcus and in the corresponding zone of the spiral ligament

As the growth develops, we can see the epithelial layer of the crista spiralis grow progressively thinner so that in this stage it appears already monostratified On the contrary the body of the crista progressively enlarges so that while on the 21th day it is clearly outlined on the 25th it looks almost like an adult s (Fig 16) Detailed observation always points out a rich capillary network which reaches almost the epithelial layer that now looks like a mosaic of cells. These cells increase in size as they approach the point where the layer reflexes on Reissner s membrane A tran verse section perpendicular to the anterior face of the crista spiralis (Fig 17) points out the rich vascular system originating from the ganglion s venous system and the lining f rmed by a line of epithelial cells having a basal nucleus and a light col ured cytoplasm reaching the free surface The intercellular limits are clearly conspicuous in the form of dark stripes also reaching the open surface Practically this will be the final aspect when the developmental stage is ended The intercellular septa will become the so called "acoustic teeth" and the spaces between these will become the interdental sulci inside which the interdental cells will lie

26 days Embryos

At this point of development the Reissner s membrane has almost completely achieved its ultimate look as a matter of fact a transverse section of the cochlear duct shows it to be very thin (Fig. 18) owing to the further flattening both of the epithelium and the mesenchyme the latter by this time being represented by a single line of rather long endothelial like cells. In our opinion the progressive thinning of both the layers forming Reissner s membrane we have been observing up to this time is probably partially at least the outcome of the compression formerly exerted by the endolymph and perilymph upon both the surfaces of the aforesaid membrane

Even the blood vessels running in the body of the mesenchyme covering the vestibular surface suffer from the consequence of the tension thinning the membrane hence quite flattened they cannot be seen inside Reissner s meml rane I ut are however distinctly conspicuous as soon as we observe on oblique or front section In this case some capillary vessels can be easily seen going through it in a radial direction sometimes bifurcating on approaching the corresponding crista spiralis

The part of lateral wall where the stria vascularis will originate is now covered with epithelial cells, somewhat shorter than in the previous stages. These epithelial cells continue in the anterior part with the epithelial cells



FIG. 17–20

lining Reissner s membrane, and in the posterior part with some cells, provided with a light cytoplasm, whose height increases the nearer they get to the floor of cochlear duct (Fig 19) The border of each epithelial cell is not well defined, whereas the basal membrane separating it from the underlying connective is, as usual perfectly clear (Fig 20) The connective shows an even more evident separation of the narrow thickly nucleated zone at the borders of the epithelium from the wide fascia of more loose connective tissue in its outer part Besides at the inner edges of the spiral ligament another layer of cellular thickening is now appearing just along the border of the cartilaginous capsule, so that a rough division in three different zones, previously mentioned by Leimgruber takes place in the ligament.

On the 26th day very important changes begin to appear in correspondence to the spiral prominence and outer spiral sulcus.

As regards the lining epithelium, we see that the cell morphology remarkably changes according to whether the cells belong to the stria or to the prominence and the outer spiral sulcus In correspondence to the

stria vascularis the epithelial cells are cubic rather small with a deeply coloured cytoplasm and a large nucleus occupying most of the cytoplasm on the contrary in correspondence to the prominence and the outer spiral sulcus, the cells are larger the cytoplasm lighter while the size of the nucleus keeps nearly unchanged The passing point from one kind of cell to the other is generally clear enough

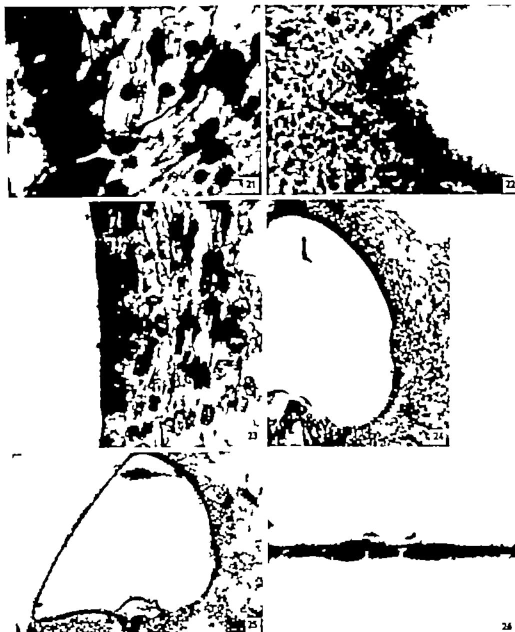
On examining with immersion lens the part of ligament bordering on the outer spiral sulcus, we remark a series of "sui generis" canals that starting from the base of the epithelial cells reach the subepithelial connective tissue sinking deeply in it These canals have an arched course with a fore concavity since generally they go towards the connective zone rich in capillary vessels forming the nucleus of the spiral prominence They have very thin connective wall and no endothelial lining This wall as it departs from the epithelium, grows thinner and thinner till it mingles with the connective tissue of the region In some parts the epithelial cells tend to penetrate towards the set of canals mentioned before (Fig. 21)

On the 26th day the crista spirali does not look very different from that on the 25th The vascular system is always as clearly evident as the arrangement in rows of the lining cells that come down without a break from the anterior face on to the lateral face and cover what will become the inner spiral sulcus moreover the cells of the epithelial lining are individually separated by dark septa. These ones should correspond to the intercellular septa dividing the rows of interdental cells. The dark intercellular septa however tend to surround every single cell, so that the result is the mosaiclike appearance we clearly see in Fig 22. The careful observation of these sections leads us to suspect that these are not mere septa of intercellular connective substance but very thin capillary branches almost sinusoids that surround the lining epithelial cell at the base

27 days Embryos

The epithelial layer covering the tympanic face of Reissner's membrane extends to the epithelial cover of the crista spiralis, but already in this stage contrary to what we observed in the first periods of development, the limit between Reissner's membrane and the crista spiralis is sufficiently clear cut

Along the lateral wall between the insertion of Reissner's membrane and the spiral prominence we can clearly recognize the region of the future stria vascularis in this zone the epithelial cover is made of only one layer of cubic or flat cells (Fig 23) having a granular cytoplasm with a roundish deeply coloured nucleus. The limits between each cell can be hardly made out while the line between the epithelium and the mesenchyme below is quite clean-cut Here and there however this border line seems to be formed by the single cell borders rather than by a distinct



F 21 26.

out any boundary line into the epithelium of Reissner's membrane while in its lower part it continues with the lighter cubic cells lining the prominence (Fig 24)

As in the former stages, the connective underlying the epithelium appears to be remarkably rich in cellular elements of long or roundish shapes moreover we observe a more conspicuous border line between the

latter zone and the wide fascia situated in the middle of the spiral ligament where the cells look more spaced The many capillary vessels of the connective tissue cannot reach the epithelium yet though appearing in its neighbourhood

The spiral prominence can be clearly distinguished from the other anatomic elements of the spiral ligament (Fig. 24) and its intimate structure is not very different from the one already described for the preceding embryo

In the outer spiral sulcus we always notice a connective thickening roughly arched in its fore part (Fig 24) corresponding to the zone of the aforementioned pseudo-canals

No remarkable changes are observed in the crista spiralis

95 days Embryos

In this last stage of embryonic development the transverse section of the cochlear duct (Fig 25) as a whole shows an aspect very similar to the ultimate one of course that is true only for the basal turn since for an instance as to the apical turn the development of the cochlear structures is still in an almost initial stage

By this time Reissner's membrane appears clearly outlined by the crista spiralis At the insertion point of Reissner's membrane moreover the large light cells forming the "vascular epithelial zone" already described by Borghesan in the grown up rabbit, are clearly conspicuous On the contrary the insertion of Reissner's membrane on the free surface of the spiral ligament has no clear boundary line between the membrane epithelium and that one of the stria vascularis The epithelial lining of the stria gradually changes into the cells lining Reissner's membrane showing only a gradual flattening of the cells and a somewhat lighter coloured cytoplasm In this stage moreover we notice that even the epithelial cells lining the tympanic surface of Reissner's membrane show though maintaining their polygonal shape a thinner cytoplasm so that their nuclei, now oval stand out like small swellings (Fig 26) i.e the epithelium gets that endothelium like appearance both Weibel and in the grown up animal Retzius had already pointed out

The lateral wall of the cochlear duct in the part corresponding to the stria vascularis, is always lined with cubic epithelial cells, whose cytoplasm distinctly granular is now more deeply coloured (Fig. 27) These cells are generally arranged in a single line only in some parts of it, especially near the insertion of Reissner's membrane we can observe some sort of stratification due to the presence of some epithelial cells with lighter cytoplasm below the superficial line All along the epithelial arch of the stria there is no real basal membrane as observed in the former stages, since in many parts the border line between the epithelium and the connective underneath appears to be rather confused Not unfrequently we find con

nective cells that leaning against the epithelium, give rise to a lowering of the basal edge Also the part of spiral ligament nearest to the epithelium shows some changes the thickly filled cellular stripe directly adjoining the epithelium gets narrower and another narrow zone with a peculiar reticular aspect of the intercellular substance separates it from the broad band of loose connective tissue placed in the center of the ligament

Blood vessels run also in the immediate neighbourhood of the epithelium (Fig 27) often touching it In Fig 28 we see a capillary vessel in a cross section leaning against the basis of two epithelial cells of the stria that show a light hollow as if to contain it. However we find no real protoplasm extensions reaching the vessels to wrap them up

In the 28 days embryo already the vessel supply of the stria takes place according to the typical ways of the vessel distribution found out and carefully described by Borghesan in the grown up rabbit. The many capillary vessels running in the region of the stria vascularis and adjoining the epithelium, even if not contained in it form a rich subepithelial vascular plexus

In the 28 days embryo we do not notice any important alteration as regards the spiral prominence the epithelial lining is made of cells having the same qualities described in the previous stages and in the connective tissue of the corresponding part of the spiral ligament the cellular elements and the blood vessels are largely present.

In the outer spiral sulcus the canal like elements previously described are present moreover we notice inside the lining epithelium some cylindrical cells with a large central nucleus and a light cytoplasm, standing out among the cells near They seem to be secreting cylindrical cells because their cellular membrane appears sometimes to be broken in correspondence to the free surface (Fig. 29)

As to the crista spiralis no important change is to be pointed out on the 28th day compared with the 27 days embryo The subepithelial capillary system is always rich and not rarely is it possible to point out some large capillary vessels differently anastomosing (Fig 30) Also the septa of dark osmophilic substance wrapping the single epithelial cells are present here.

New-born Rabbit

In the newborn rabbit Reissner s membrane appears to be fully realized both in the basal and apical turn

The stria vascularis is very similar to the 28 days embryo previously described. However we find some alteration both in the epithelium, whose cells tend by now to spread down towards the vessels, and in the connective underneath that shows an increased pigmentation in the zone adjoining the epithelium of the stria. Between the mentioned zone and the wide band of loose connective tissue placed in the middle part of the spiral ligament,

we find a narrow band marked by an almost net like appearance of the intercellular substance

The region of the spiral ligament corresponding to the prominence and to the outer spiral sulcus keeps the same histomorphological qualities described in the previous stage the villiform structure of the spiral prominence is now more evident

Even the crista spiralis has reached in the newborn rabbit its ultimate stage of development Generally we can distinctly make out the rich vascular system whose capillary vessels run close to the lining cells, both of the anterior face and of the inner spiral sulcu (Fig. 31)

16 hours Rabbit

In a transverse section of the cochlear duct (Fig 32) 16 hours after birth we clearly see the Corti organ that has not reached the complete maturity yet with its hair cells of first second and third row the tectorial membrane adhering in part to the Corti organ the Reissner's membrane slightly swelling towards the lumen of the cochlear duct probably because of the haematic effusion existing in the scala vestibuli the crista spiralis where Reissner's membrane and the tectorial membrane are inserted

The stria vascularis is now looking like a dark band hollow towards the lumen of the cochlear duct and larger than in the last days of embryonic life (Fig 32) Going from the inside out first we observe a superficial layer of epithelial cells marked by deeply coloured nuclei and cytoplasms. Some of these cells, having disappeared their basal membrane stretch into the deepest layer often wrapping the rather numerous capillary vessels with their protoplasmic extensions (Fig 33) The cellular elements that mixed with the capillary vessels form a second layer below the superficial epithelium (Fig. 34) appear to derive on the contrary from that zone of connective thickening described in the 28 days embryo as directly adjoining the epithelium (Fig 27) Below the superficial epithelium together with these cells and the vessels, we also find cells with lighter cytoplasms whose epithelial origin had been pointed out in the last period of embryonic development Outward just next to the sharp border line between the stria and the spiral ligament we notice other cellular elements, rather spaced and having big, rather light nuclei (Fig. 34) They are presumed to be some connective cells belonging to the thin layer whose intercellular substance observed in the embryo in its last stage of development had that typical reticular appearance

The stria vascularis differentiates from the spiral ligament because of a peculiar pigmentation of greater cell and vessel density and because of the presence of a thin defining membrane of connective origin endowed here and there with oval and dark nuclei

The spiral prominence is quite conspicuous and juts clearly enough into













Fig. 27–32.

the cochlear duct (Fig 32) At this point the stria almost splits as the most superficial stratum of cubic cells continues into the layer of epithelial equally cubic cells that line the prominence the deepest stratum, on the contrary mingles with the texture of the prominence itself This finding is far from being transient since it is often found in the adult animal (Borghesan) The posterior part of the epithelial lining then continues with big light epithelial cells that gradually descend toward the spiral crest defining and forming the outer spiral sulcus

In correspondence to the spiral prominence the connective tissue of the ligament looks thicker and such thickening, unlike the one we see next to the cartilaginous capsule is due to the many capillary vessels crowding in the connective tissue of the zone Several of these vessels have red corpuscles in their lumen

Observation at greater magnification shows more interesting details (Fig 35) The prominence is lined with a layer of epithelial cells growing taller and taller as they approach the outer spiral sulcus the body of the prominence appears to be formed of connective tissue rich in nuclei and capillary vessels, whose wall are so thin they can be made out with difficulty In side the capillary vessels we often notice red corpuscles, many of which look lengthened and compressed as they have to fit the small gauge and the meandering of the vessel lumen

In correspondence to the outer spiral sulcus, right below the lining cells, we can point out a "sui generis" connective thickening that is presumed to originate from the basal part of the epithelial cells, and to sink down as roots towards the region of the spiral prominence The lining cells are more irregularly arranged since some of them tend to go deep into the connective tissue below It is worth noting that no cellular border line is conspicuous the positions of the single cells are marked by their own nuclei. In the superficial connective tissue we notice some stripes or bands of connective thickening that fade away into the connective tissue of the ligament Far from the lining epithelium of the surface and all along the connective stripes we see some clusters of nuclei belonging to epithelial cells, that seem to follow the connective stripes. The whole of these connective-epithelial formations stand right behind the body of the spiral prominence

On observing this zone we have a clear vision of epithelial cells sinking into the connective tissue of the ligament as if following prearranged paths Actually it is not a question, as some authors maintain of epithelial cells spreading some cellular branches into the connective below but of real epithelial cells moving inside the spiral ligament where often they enter into connection with blood capillaries (Fig 36) Here the connective tissue by its fibres thickening in a radial direction seems to mark out some attraction lines appearing like darker zones, in comparison with the lighter looking zones of connective tissue nearby (Fig 37)

The final outcome of all these changes inside the spiral ligament and its



FIG. 33–38.

lining epithelium is to achieve the anatomic structure in its ultimate aspect such as we observe in the seven days rabbit

The crista spiralis, in the 16 hours rabbit has practically the same appearance and anatomic characteristics of the newborn rabbit

7 days Rabbit

In the first week after birth the stria vascularis reaches its ultimate look In the first place from the insertion of Reissner's membrane to the spiral prominence we see a diminution of the stria thickness due in our opinion to a sort of retraction into the subepithelial stratum of the stria itself Moreover through a greater magnification (Fig. 38) we realize that intimate relations exist between capillaries and the branches of the epithelial cells these ones drift inward with protoplasmic expansions, as well as the extensions of the lighter cells, standing at the base of the stria branch out towards the surface The relationship between the epithelial lining and the layer below of mostly connective origin looks much more intimate than in the former stages the outcome is such a complex structure as to make it difficult by now especially if you did not follow the gradual stages of development to make out the nature of the different elements forming the stria

At the end of the first week of life even both the spiral prominence and the outer spiral sulcus have reached their final aspect

In the texture of the spiral prominence we can clearly see the epithelial vascular villi maintaining the previously described structure while the zone of spiral ligament corresponding to the outer spiral sulcus has further improved. As a matter of fact we can slowly make out inside those solid epithelial cords, that from the 20th day of embryonic life keep branching out from the superficial epithelial lining to sink in the connective tissue some light spaces, extending more or less in a radial direction, that can be classified as *lacunae or canaliculi covered with epithelial cells* morphologically similar to those forming the superficial lining. This aspect is clearly evident in Fig 39 where besides the canaliculus (A) at the end of it we can recognize an epithelial cell (B) identical to the light epithelial cells of the outer spiral sulcus (C) and several blood capillaries in a cross section set around the canaliculus itself (D)

The crista spiralis, after seven days of life has the same characters of the adult crista

It is interesting to examine that part of connective tissue acting as a floor to the interdental sulci, and which is generally considered to be formed of a thin layer of thick crammed connective tissue having no peculiar quality Here we can point out (Fig 40) a network of canals and spaces of variable diameter that often get into very intimate connection with the floor of the interdental sulci In the inner spiral sulcus, these canals, lined with cells, have a medial direction towards the body of the

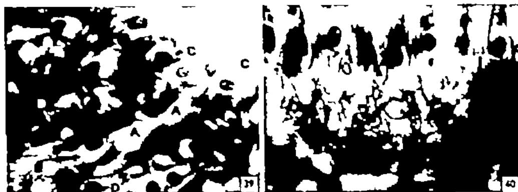


Fig. 39–40.

crista, where a very rich vascular system is always present The epithelial cells situated in the interdental sulci do not show any sharp cytoplasmic limits.

SUMMARY AND CONCLUSIONS

From the previous observations it appears that both mesenchyme and epithelium take equal part in the process of formation of Reissner's membrane

Already in the 21 days embryo, since the formation of the scala vestibuli a layer of mesenchymal cells thickens at the inner edges of it and therefore also towards the anterior wall of the cochlear duct, made of one layer of epithelial cells of cubic form This is the first outline of Reissner's membrane Later on, the epithelial layer flattens more and more tending to acquire a peculiar endothelium like aspect and at the same time the mesenchymal layer lining the vestibular face of Reissner's membrane grows thinner On the 28th day of embryonal life the formation of Reissner's membrane is to be considered by now complete

These results allow us, then to support what several authors have been maintaining up to this time, that is, that in the grown-up rabbit, Reissner's membrane appears to consist of two layers, the mesenchymal layer and the epithelial layer both endotheliform The mesenchymal layer is always separated from the epithelial one by a distinct basal membrane Probably the latter corresponds to that very thin intermediate layer pointed out by Gottstein, Kolmer and other authors and by nearly all of them described as homogeneous and amorphous

In the embryo's Reissner's membrane we took note of the presence of blood vessels with a radial course in the body of the mesenchymal layer Finding blood vessels in Reissner's membrane is not to be considered though a report of only embryonic nature since it was remarked also in

the post natal period and as Borghesan previously observed, in the adult rabbit Also Shambaugh and Nabeya found blood vessels in Reissner's membrane not only in the rabbit but also in other animals while in man the absence of blood vessels has been observed by Kolmer Scuderi and Del Bo

The study of the various stages of development of the stria vascularis has pointed out the different embryonic derivations, partly from the epithelium, partly from the connective tissue of the elements forming the stria of the adult rabbit

The epithelial layer lining the external wall of the cochlear duct and which consists of only one layer of cells, cylindrical at first then shorter and shorter appears to be sharply separated by a clear-cut basal membrane from the connective tissue below whose capillaries grow more and more numerous and closer to the surface as the development goes on Towards the end of embryonic life (28th day) however the marking line between epithelium and connective tissue begins to fade away in some parts until it cannot be made out at all in the newborn rabbit

At the same time between a thin connective zone adjoining the epithelium and the rest of the spiral ligament a new border line appears that will be later the final limit of the stria vascularis.

The connective layer that towards the end of embryonic life we find to be directly adjoining the epithelium has become an integral part of the stria after the birth In it we can clearly make out an inner layer rich both in vessels and in cells with deeply coloured nuclei and an outer layer marked by the presence of cells with rather big nuclei lacking in chromatin

Hence the layer that in the stria vascularis stands below the epithelial lining, may be considered to be of connective derivation though we can possibly find various elements of epithelial nature in it as the protoplasmic extensions branching out of the surface and the cells coming from the basal limit of the epithelium

The elements forming the stria vascularis are therefore of different embryonic derivation In our opinion the stria, though being also a vascular epithelium owing to the intimate connections between epithelium and capillary vessels, cannot be regarded at the same time as just a mere vascular epithelium because of the presence of many connective cells between the epithelial elements.

It is worthy noticing then that the vessels almost to the end of embryonic life appear separated from the epithelial layer lining the external wall of the cochlear duct Only later they come into more or less intimate relation with it In the embryo then we neither find those peculiar vascular-epithelial connections that mark the stria of the adult animal, nor the two basic conditions to which a secreting function of the stria vascularis is to be ascribed do subsist that is, plenty of capillary and a close relation between the latter and the epithelium

Furthermore Kawano (1922) during the embryonic development of the

stria vascularis, has noticed the complete involution of the intercellular Golgi apparatus which on the contrary is quite developed in the adult s stria and which changes in relation to the secreting function (Fleandt and Saxen) In our opinion then, the stria vascularis, during the interior life, is not likely to secret endolymph A humoral function during the em bryonic life may be ascribed according to Borghesan to the spiral canalicular system whose maturation is earlier than the maturation of the stria vascularis.

As to the spiral prominence embryonic observations show that it ac quires its own individuality on the 21st day of embryonic life At the end of the growth it is formed of a complex capillary vascular system which connects with peculiar canalicular structures, lined with epithelial cells, that originate from the lining cells of the outer spiral sulcus, so that a characteristic villi form structure comes out

From the 21st day of embryonic life to the end of growth some in teresting changes take place in that part of the spiral ligament which corresponds to the outer spiral sulcus. We notice that some groups of epithelial cells, looking like solid chords inside which as development goes on and before birth canal like lumina come into being, move into the whole of the spiral ligament and spiral prominence Then we observe the process of formation and perfection of a sui generis" canal system, which much resembles the one previously described in the adult by Borghesan which he called "spiral canalicular system"

It should be the task of the spiral prominence, during the embryonic stage when the stria vascularis is not working, to produce nourishing substances for the spiral papilla these ones should be conveyed towards the cochlear duct and the spiral ligament by the spiral canalicular system (Borghesan 1965)

Recent histo-chemical researches would support this assumption. As a matter of fact Vosteen (1961 1964) has demonstrated here the presence of succinic dehydrogenase which proves an intense metabolic activity and Rauch (1964) points out the possibility that the anatomic structures of this zone might play an important part in the adjustment of the composi tion of endolymph.

The crista spiralis begins to differentiate on the 16th day of embryonic life in the form of a mesenchymal thickening in correspondence to the posterior medial corner of the former cochlear duct. In it we notice many early capillaries in close relationship to the epithelial lining cells that, at first have a pluristratified arrangement Later on, they gather in one layer and line up in rows limited by thin connective stripes that thickening by degrees, define real groves inside which the epithelial cells are kept. Such changes take place both on the fore wall and on the lateral wall of the crista spiralis

At the end of development, the crista spiralis appears to be formed, going from the surface downwards, of a "sui generis" canal system that

from the insertion of Reissner's membrane goes sideward to the vestibular rim where it bends in an anterior posterior direction coming to an end near the tympanic rim The canals of the system are occupied by epithelial cells arranged in one layer while their flooring borders on a connective layer with a sieve-like aspect due to the presence of several canals lined with epithelial cells. These canals, in their turn come into relationship with the rich capillary system of the body of the crista spiralis and appear to be more conspicuous in correspondence to the lateral wall

In conclusion, this research supports the embryological studies of Van der Stricht O about crista spiralis as well as Borghesan's anatomical description and functional deductions for the cochlear duct is such as to give the endolymph since embryonic life a wide absorbing surface and a rich defluxion network towards the venous system of the Rosenthal canal

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S U P P L E M E N T U M 224

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HELSINKI, JUNE 27—30 1966

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MERCATORS TRYCKERI

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MEETING OF THE COUNCIL OF THE SCANDINAVIAN OTO-LARYNGOLOGICAL SOCIETY

The meeting took place at the Palace Hotel on June 27th, 1966, at 12 o clock noon.

The following members of the Council were present. H Ewertsen and E. Zwergius representing Denmark T Leegaard representing Norway C-A. Hamberger and R Rudberg representing Sweden, U Siirala and T Palva representing Finland, and the Secretary of the Congress B. Grahne.

The President of the Congress, Professor Urpo Siirala was elected Chairman.

The election of Bertel Grahne as Secretary to the Congress was approved

E. Zwergius suggested that the next Congress should be held in Denmark 1969 The Council accepted the Danish invitation with gratitude. It was proposed that for that Congress Professor H. C. Andersen should act as President and H K. Kristensen as Vice-President. This proposal was carried unanimously by the Council.

It was decided that the annual subscription to the Scandinavian Oto-Laryngological Society should remain unchanged at the equivalent of 25 Swedish Kronor in the currency of the various countries, with, in the case of Finland, a free choice of Kronor currency

Certain changes in the wording in the statutes of the Scandinavian Society concerning the membership of Island were discussed.

The Council discussed the Finnish proposal that, parallel with the Scandinavian languages, English be accepted as an alternative congress language.

Certain changes in the statutes of the Scandinavian Oto-Laryngological Society were suggested. It was agreed that these changes be brought up for decision at the Business Meeting of the Congress.

Business Meeting of the Congress

This meeting took place in the Porthania lecture halls at the end of the session on Thursday June 30th.

The President announced the invitation from the Danes for the next Congress, to be held in Denmark in 1969 The Congress accepted the invitation and agreed unanimously to the Danish proposal that the next Congress Committee should consist of Professor H C. Andersen President Professor H K. Kristensen, Vice President, and dr Ole Bentzen, Secretary The place and date of the Congress were left to this Committee which should also decide upon and draw up the programme It was proposed by the Danish members that phoniatry should be included among the subjects to be discussed at the next Congress.

The suggestion that Lnglish should be accepted as an alternative congress language did not win support

The Congress approved the statutes of the Scandinavian Oto-Laryngological Society in the following form

§ 1

The object of the Society is to promote oto-laryngological research in the Scandinavian countries (Denmark Finland Iceland Norway and Sweden) The Society through its counsil strives to maintain and develop contacts between the societies in the various Scandinavian countries, by means of Scandinavian congresses and in other ways.

§ 2

Each member of the oto-laryngological scientific societies in the respective countries is automatically a member of the Scandinavian Society

§ 3

The Society is conducted by a council consisting of two members from each country (one of whom is the chairman of his own country s society), plus a chairman The other member and a deputy member are elected by the respective societies and remain in office for two congress periods. They cannot be relected The chairman for the next congress becomes the chairman of the council at the time he is elected until the election of the next congress chairman A new working period begins at the conclusion of each congress.

§ 4

The council will take up a subject for consideration at the request, in writing or orally of at least two members of the council or of a country s society

The council can also discuss matters of interest to all Scandinavian countries which do not concern Congress preparations. When members are summoned to a meeting the expenses are defrayed by the society in each country

§ 5

As a rule a congress is held in one of the Scandinavian countries every three years.

Non-members of the oto-laryngological societies in all Scandinavian countries can take active part in the congress. Applications to be sent to the Boards of the societies in the respective countries.

§ 6

A congress committee consisting of three members, a chairman, vice-chairman and secretary-general, is in charge of congress arrangements.

The committee appoints a cashier two accountants and possibly other assistants. One of the accountants should be a chartered accountant.

The council first propose and the congress elects the committee for the next congress from among the members for the country where it is to take place If a member of the committee is prevented from attending, the council may elect a deputy from the same country

§ 7

The congress committee is responsible for the distribution of the congress report and for the accounts, to be sent to the council not later than six months after the report, for forwarding to the societies of the respective countries.

§ 8

An annual fee for each member is charged to the respective societies to cover the secretarial expenses of the congress (including printing costs), the amount of this fee is fixed by the council. Members of the congress pay their own expenses incurred from social activities during congresses.

§ 9

The annual fees collected in the interval between two congresses will be made available to the congress committee.

§ 10

A meeting of the council and of the congress committee to be held immediately before each congress for the purpose of discussing the affairs of the Society

§ 11

The congress appoints the time and place of the next congress, discusses the subjects to be dealt with there and can also discuss other matters of interest to the Society Abstracts to be sent to members not later than one month before the date of the congress

§ 12.

Amendments of rules are accepted by the congress by simple majority after having been discussed by the council and by the society in each country

Professor H C. Andersen thanked the Committee and the Finnish hosts for all they had done to make the Congress a success and bade the members welcome to the next Congress in Denmark in 1969

Entertainments during the Congress

On Monday June 27th, at 6 p.m. the members and their ladies were invited by the City of Helsinki to a reception held at the new block of Municipal Offices.

On Tuesday June 28th, one group of ladies visited the porcelain factory »Arabia» and another group the National Museum, after which both groups went on a sight seeing tour by bus. The ladies had lunch together and attended a fashion show The afternoon programme included a visit to the Sinebryehoff Art Gallery In the evening all members of the Congress and their ladies were entertained in private homes by their Finnish hosts.

On Wednesday morning June 29th, the ladies paid a visit to the Gallen-Kallela Museum »Tarvaspää» and then members and their ladies were entertained to lunch at the Palace Hotel.

A banquet was held the same evening at the Kalastajatorppa — Fiskartorpet.

Bertel Grahne

Secretary

THE DEVELOPMENT OF OTOLARYNGOLOGY IN FINLAND

Urpo Siirala and *Aino Nikupaavo*

Helsinki, Finland

From the Otolaryngological Hospital (Head. Prof. Urpo Siirala),
Helsinki University Finland

The actual beginning of clinical otolaryngology in Finland goes back over 75 years: the first outclinic designed especially for otolaryngological cases started to operate in conjunction with the Outpatient Clinic of the Surgical Department of the General Hospital in Helsinki in 1891 A surgical hospital intended mainly for patients with ear nose and throat diseases was started as a private undertaking in 1900 and run under the direction of its owner Arthur af Forselles, who had been appointed Docent in Otology in 1896. In 1907 he became the first holder of the new Chair in Otorhinolaryngology founded in the University of Helsinki in 1903. The year 1908 marked the start of the Otolaryngological Department of the General Hospital of Helsinki, in a building rented by af Forselles. It had taken almost three decades for the plans concerning special university instruction and the establishment of a separate hospital department to mature and the above result to be achieved. Others besides af Forselles had advocated such a plan, for example G. Asp, Professor of Anatomy and J A. Estlander Professor of Surgery in the eighteen-seventies; and above all M W af Schultén, Professor of Surgery in the eighteen-eighties and -nineties.

However otolaryngology in Finland can point to much earlier »milestones» if one traces its early history back to its roots. These can be found among the so-called »candidate theses» presented as proof of learning in the highly esteemed Academy founded in Turku in 1640

The earliest of these theses was written under the guidance of Professor Georg Alanus, a native of Jomala in the Aaland Islands, who held a professorship in 1640—48. The title-page indicates that the thesis »De sensibus externis» was defended by Johannes Ketarmannus, from the province of Upper Satakunta, in 1647 This is the first thesis published in Finland dealing with the functions of man s various senses and with the structure of the sense organs.

The fifth Professor of Physics at the old Academy of Turku was Petrus Hahn — the most interesting figure, from the viewpoint of otolaryngology during the first century of the Academy's existence. He had come over from Sweden to study at the Academy When appointed Professor of Physics in 1683 his salary should, according to the custom of those days, have included a church benefice in Finland. This, however he was unable to have since he had no knowledge of the Finnish language, so he was promised the position of Chief Librarian to the Academy instead. Though he was not particularly interested in this task, the arrangement offered him opportunities for successful work, for he began — with great skill — to direct the preparation of theses at the Academy No less than

125 were completed during his period of office, and four of them were on subjects related to otolaryngology The first dealt with the human senses in general and was entitled »De sensibus hominis». Andreas Lundius defended this thesis in 1690- It comprised 28 pages. It was followed by theses dealing in greater detail with the special senses, the first being on that of hearing· »De audiendu sensu» (1696) by Olaus Junholm. This work, already 270 years old is a fine example of how greatly hearing was esteemed as a means of communication at the very beginning the writer launches into eloquent praise of the wonders of the sense of hearing At the same time the 40 pages of the thesis contain all the information then available about the auditory apparatus.

One cannot speak of the practice of medicine in those early days since the practical facilities were lacking There were neither doctors nor hospitals. Medical care therefore was in charge of barber-surgeons and Nature healers. Remedies used in the old days by the Finns to relieve earache included (according to Armas Ruotsalainen s »Popular cures for ear diseases») the following· breast milk, milk mixed with spirits, black sheep s wool inserted into the ear onion fomentations, and hare s urine. Incantations of various kinds were also used to restore hearing

Research proper into aural diseases and medical otology did not start until the eighteen-hundreds, when, after the destruction of Turku by fire, the old Academy became the University of Helsinki and hospitals became available in the new capital.

So far we do not fully know what induced Lars Henrik Törnroth (1796—1861) to take up the study of inflammations of the middle ear Both the first part of his research work, his doctoral thesis (1832) and the second part of the work, for the Chair of Surgery and Obstetrics (1837) were concerned with middle ear inflamma tions and the their treatment and were based on personal experience. Törnroth s two theses were criticized on the grounds that their subject matter appeared of minor importance from the point of view of general surgery and that they con tained no reports of his own cases. Compared with other theses from the same period they did, however contain a remarkable amount of knowledge gathered at home and abroad. Professor Törnroth s name will also retain its place in the history of otology by reason of a fact worth mentioning here old programmes of the University of Helsinki reveal that, alongside his other lectures, he also delivered special lectures on ear diseases during a period of three years (1843—45).

It is not possible in this context to treat in more detail other events connected with the study of ear nose and throat disease in nineteenth-century Finland It might be worth while, however to state that, in addition to the publications mentioned above, there appeared a number of other treatises and theses concerned with this particular branch — among them one on the sense of taste (A J Palmberg) — as well as scores of articles and reports. The first articles on ear operations, written by A af Forselles and H. W Zilliacus, appeared at the end of the century Finnish physicians made trips to various European centres for otorhinolaryngological research and attended congresses etc., thus enabling themselves to keep abreast of developments. New instruments were demonstrated at meetings of the Medical Association fairly soon after they were first devised. The per

forated ear speculum (devised by F Hoffmann) was demonstrated by Professor E. J Bonsdorff in 1853 and Wiese s ear speculum in 1854 by Professor (Archiater) L. H. Törnroth. Czermak s laryngoscope was first shown in Finland by Professor Knut Sirelius in 1859 But it was not until the end of the century that doctors began to devote themselves to private treatment of ear nose and throat diseases.

At the turn of the 19th to the 20th century there were four medical men in Finland who had specialized mainly in otolaryngology They were. H W J Zilliacus, S A Granberg, G A Tollet and A af Forselles.

Ten years later the number had increased to 12. Further additions to the list are K. A. Elmgren, E. A. Tollet G A. Björkqvist, A. E. Bonsdorff T G A. Aschan, H. M. von Fleandt, and E. E. V Suolahti. At that time the specialists qualifications had not yet been fixed. each physician could freely devote himself to the branch he took most interest in.

Already there was also one physician, in Helsinki, who had had specialist training abroad in speech and voice disorders — a woman by the name of Rauha Hammar

When the Finnish Otolaryngological Society was founded in 1922, 18 physicians joined the same year which figure indicates the number of specialists at the time. Throughout the 1930 s the number of otolaryngologists remained almost unchanged, at just below 30 Right up to 1951 their number had not increased appreciably since the membership was then 35 During the next ten years, however a decisive change for the better took place: by 1961 the figure had risen to 76 During the last five years the increase has been steeper still, owing in part to the fact that the Society now accepts as a member every doctor who has a regular appointment for specializing at an approved ENT teaching hospital. There are now 95 specialists including the trainees in the speciality and of this number 45 are in Helsinki. There are four phoniatricians: 2 in Helsinki, one in Oulu and one in Jyväskylä In addition there is a Phoniatric Outpatient Clinic, led by an otologist, in Turku.

We have attempted here to summarize briefly the development of otolaryngology in Finland, covering a period of over 300 years. In the course of the last 20 years, the number of otolaryngologists and of available positions has increased to the extent that the most densely populated parts of the country can be said to be fairly well served. During this period two more Chairs have been created, and academic teaching is now offered at three universities.

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ORAL MEDICINE

J J Pindborg

Copenhagen

Oral medicine is defined as the science which deals with the oral manifestations of systemic diseases. Only three groups of systemic diseases will be dealt with: Blood dyscrasias, dermatologic disorders and systemic infections. In the group of blood dyscrasias the oral aspects of anemias, neutropenias, and leukemias will be discussed. The group of dermatologic disorders comprises pemphigus, pemphigoid, erythema multiforme exudativum and hereditary epidermolysis bullosa. Finally viral infections (herpetic gingivostomatitis, herpes zoster), bacterial infections (gonorrhoea, syphilis), and mycotic infections (moniliasis) will be discussed.

ORAL LEUKOPLAKIA AS A PRECANCEROUS CONDITION

J J Pindborg

Copenhagen

Based upon a material of 250 patients with oral leukoplakias some new concepts are presented. The leukoplakias are divided into 1) homogeneous, slow-growing lesions characterized by hyperortho- or hyperparakeratosis and 2) speckled, probably premalignant lesions clinically exhibiting white and red areas side by side. Histologically the speckled leukoplakias are often associated with epithelial atypia. A number of oral leukoplakias are associated with monilial infection. The results of an 8-year-follow-up study are reported. Malignant transformation of oral leukoplakias occurs in about 5% only

STOMATOLOGY WITH SURGICAL VIEWPOINTS

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Stomatologic surgery is borderland between many different pecialities such as oral surgery to-rhino-laryngology and plastic surgery I order t obtain the best results from the urgical treatment a close team-work between those different specialities is often needed. In this introductory speech different principles of treatment are discussed from odontologic and otologic aspects.

From the surgical point of view stomatology includes dental surgery and jaw surgery as well as surgery of the oral cavity Dental surgery — the term formerly used — is inadequate Since it applies to interventions on the tooth or dental organ, it corresponds to *restorative* dentistry Consequently in Sweden, the term dental surgery has been replaced by oral surgery according to the custom in the U.S.A

Stomatological surgery is thus a borderline field between several disciplines, such as oral surgery otology and plastic surgery In many cases, teamwork between different specialists is required to achieve the the best results of surgical treatment

It therefore seems to be my task at this Congress to cover the fields in which teamwork between odontology and oto-rhinolaryngology is an absolute prerequisite — in which we are thus dependent on the expertise of both these specialities.

As far as congenital malformations are concerned, surgical treatment of cleft palate in Sweden has now been taken over by plastic surgeons. Despite this, an extremely important role is played in the treatment of this malformation by the specially trained dentists, the facial prosthetist.

On the other hand another usually congenital malformation, mandibular prognathism or protrusion is treated at several otological clinics in Sweden. Prerequisites for satisfactory results are repair of carious teeth analysis of occlusion and an apparatus for fixation of the jaws At the Departments of Otolaryngology and of Oral and Jaw Diseases, Karolinska Sjukhuset, 201 operations for mandibular prognathism have been performed since 1952. The age distributions shows that almost half of the patients were around 20 years old It is not, in fact, until this age that the jaw are definitely formed. In every case operation consisted of osteotomy of the mandibular ramus, between the incisura mandibulae and the mandibular foramen. We do not perform osteotomy of the body of the mandible. Although we have not yet made a complete follow-up study of the case material this has been planned. We have had not a single case of primary complications in the form of haemorrhage or facial paralysis, of which the incidence is stated to be 5 % in some series. We have operated on a few patients in their fifties. The indication has been that the patient was unable, because of mandibular prognathism to wear a serviceable prosthesis. In these cases, we have used fixation with Gunning-type splints, by means of circumferential wiring around the mandible and alveolar wiring through the alveolar process of the maxilla

TABLE 1

OPERATIONS OF MANDIBULAR PROTRUSION

Age	Number
—20 years	46
21—30	94
31—40	53
41—	11
Total	204

Men 102
Women 102
Total 204

The treatment of fractures of the jaw is of paramount otological interest. In Sweden about 1300 persons die every year in traffic accidents. It is calculated that about 20 % of them could have survived if proper treatment had been given at the site of the accident. We have in fact, launched as slogan »ABC of traffic accidents» in which *A* denotes air passage, *B* bleeding and *C* circulation. The otologist is the specialist who is responsible — naturally in collaboration with the anaesthetist — for the maintenance of a free airway. Table 2 shows the age and sex distribution in 330 fractures of the jaw that we have treated during the past three years.

TABLE 2

FRACTURES OF THE JAW: AGE AND SEX DISTRIBUTION

Age (years)	Men	Women	Total
<10	7	6	13
11—20	43	26	69
21—30	52	23	75
31—40	46	15	61
41—50	45	19	64
51—60	21	11	32
>61	11	5	16
Total	225	105	330

It is evident from the table that no less than 25 % of the patients were under 20 years of age; in my opinion this is a somewhat frightening figure. Obviously the final treatment of damage to the face and jaws often requires intimate cooperation between various specialists, such as the oral surgeon, facial prosthetist, otolaryngologist, plastic surgeon and neurosurgeon. But I believe that the organization we have built up for treating these cases functions in the proper way. Thus, a serious case of damage to the face and jaws in given primary care by the physician on duty at the Department of Otolaryngology. Other specialists are then called into consultation.

The largest number of fractures of the jaw involve the lower jaw and amount to more than 80 %. Combined fractures (of both lower and upper jaw) comprise about 3 %. Although lower jaw fractures seldom require *surgical* treatment, there are two important exceptions. I have already mentioned one of them, i.e., edentulous patients, in whom alveolar and circumferential wiring are done. The other is the

important group of cases with an edentulous posterior fragment in which inter osseous wiring is required

Upper jaw fractures can be immobilized with a plaster of paris head cap or surgically e.g around the zygomatic arch An important category of upper jaw fractures — which are not, however included in the present figures — consists of fractures of the zygoma Since in most of them, operation is performed through the maxillary sinus as a Caldwell Luc operation they pertain to the field of otolaryngology

This brings us to the large significant field consisting of surgical interventions on the nasal accessory sinuses that are of stomatological interest. I have already mentioned trauma I shall now discuss other diseases that are within the scope of this opening paper They comprise dental sinusitis, permanent fistulas, large cysts of the upper jaw and tumours, both benign and malignant

From the aetiological point of view sinusitis can be divided into two groups, one of which is the genuine or primary form, usually denoted as rhinogenic. The other group consists of secondary extending sinusitis, usually denoted as dental. The incidence of dental sinusitis reported in the literature varies A review of our clinically treated material, consisting of 1702 cases, showed that 12.1 were of dental origin.

Root fragments that have been displaced into the maxillary sinus on attempts at extraction should be removed as soon as possible. They should not however be extracted via the alveolus. This is because there is then a risk of transmitting infection through the oral cavity Moreover an attempt to enlarge the opening may result in a large fistula Consequently a tooth root dislodged into the maxillary sinus should be extracted by an exploratory Caldwell-Luc operation

As far as permanent fistulas to the maxillary sinus are concerned, many operative techniques have been recommended During the past few years, we have applied the method described by Wassmund and Rehrmann A follow-up study of the operative results in permanent fistulas to the maxillary sinus disclosed that when we were able to perform the primary operation, healing occurred in all but one case The results were, on the other hand poorer in cases in which operation had been performed earlier by some other method

With respect to surgical treatment of large intrasinusal cysts, an excellent survey was given by Harry Björk (1910) among others. Two methods are available for operating on such cysts. Partsch 1 and Partsch 2. In the Partsch 1 operation the cyst is converted into a recess in the oral cavity This method has several draw backs. Food debris and saliva are apt to collect in the recess. Although this can be prevented to some extent by packing or a prosthesis, the packing must be con stantly changed and the cavity irrigated daily Finally with this technique no histological examination can be made of the *whole* mucosa of the cyst. It is true that the risk of malignant degeneration is relatively slight, but our series never theless contains five cysts in which such malignancy took place; 3 involved the upper jaw and 2 the lower I am therefore fully in agreement with Harry Björk's statement that large intrasinusal cysts should undergo radical Caldwell Luc operation

The most common symptoms and signs of cancer of the paranasal sinuses are the same as those of sinusitis. However in a series of 648 cases of sinusal cancer treated at the Department of Otolaryngology Karolinska Sjukhuset, and Radiumhemmet, symptoms from the oral cavity were present in no less than 10 %, of which 3.7 were located to the teeth.

Tumours of the jaws are divided into osteogenic and odontogenic The tooth is formed from both the ectodermal and the mesodermal anlagen. Adamantinoma — *or preferably ameloblastoma — derives from the ectoderm whereas fibroma* and cementoma derive from the mesoderm Finally various forms of odontoma are formed from a mixture of mesodermal and ectodermal cells.

Benign tumours of the oral cavity seldom present any major surgical problems. They can, as a rule be radically excised

A few facts concerning the various forms of epulis must nevertheless be emphasized. They are divided into granulomatous, fibromatous and giant-cell epulides. The last-mentioned are sometimes denoted as true epulides. If histological examination discloses a giant-cell epulis, the serum content of calcium and phosphorus should be determined, since the cause may be an adenoma of the parathyroid gland Epulides have certain characteristic properties. They are much more frequent in women than in man. Radical operation is absolutely necessary in view of the considerable tendency to local recurrence

Treatment of malignant tumours of the jaws and oral cavity often necessitates *intimate collaboration between various specialists. This applies, for instance* to fixation and reconstruction in connexion with surgery

In extensive resection of the lower jaw deviation can be prevented by suitable intermaxillary fixation After extensive resection of the upper jaw well-made facial prostheses can allow the patient to resume work, and to be socially rehabilitated

This brief survey is merely an attempt to illustrate some aspects of surgical stomatology It is incomplete and cannot be otherwise in the space of 30 minutes Thus, time has not permitted demonstration of e.g preprosthetic surgery jaw joint complications with trismus, ankylosis, crepitations and other symptoms with otalgia. It might also have been of interest to make some mention of the treatment of osteitis and osteomyelitis of the jaws. These conditions should, however generally be treated conservatively and seldom require surgical intervention.

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ORAL CARCINOMA IN CASES OF LEUKOPLAKIA OF THE ORAL MUCOSA

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A material of leukoplakia in the oral cavity is gone through and the incidence of cancer in the oral cavity is discussed in a statistical analysis.

Leukoplakia is a patch in the mucosa characterized histologically by hyperplastic and hyperkeratotic changes of the epithelium. In a minority of cases cytologic evidence of premalignancy may be observed, such as an increased number of mitotic figures, great variation in the size and shape of the cells and the chromatin content of the nuclei and dyskeratosis.

That malignant transformation occurs in some cases of leukoplakia is generally agreed but estimates of the proportion of such cases range from 2.5 to nearly 100 per cent. In an analysis of the reports of 28 authors, McKee and Cipollaro (1937) found an average incidence of 30 per cent, but more recently this figure has been questioned (Shafter and Waldron 1961).

The purpose of the present work was to study the incidence of oral carcinoma in patients followed after a diagnosis of leukoplakia of the oral mucosa or the lip. In the calculation of the prevelance of malignancy account was taken of the follow up period for each patient.

Material and methods

Between 1920 and 1960 833 patients were seen at Radiumhemmet for alterations in the mucosa of the oral cavity or the lip diagnosed by the examining physician as leukoplakia. Fifty of the patients were followed for less than one year and were not available for examination when the case series was compiled, none of them is known to have developed oral carcinoma. The remaining 783 patients — comprising 94 per cent of the series — were followed from 1 to 41 years, the mean follow-up time was 11.7 years. Of these 783 patients 523 were men and 260 women. In 286 cases the diagnosis was supplemented by histologic examination. Surgical removal of the leukoplakia was performed in 313 cases.

The patients were followed by annual examinations at Radiumhemmet or the Department of Otolaryngology, by correspondence with the patients or the physicians following them and by examination of autopsy reports or notes from other hospitals where the patient was treated during the follow-up period. In 1965 this follow up was supplemented by 2 questionnaires sent to the patients and by an examination of 117 of the patients, supplemented with biopsy examinations of the oral leukoplakia if deemed necessary.

An oral tumour was defined as a discrete, clinically or histologically malignant neoplasm situated on the lip, tongue, floor or elsewhere in the mouth. Tumours of the pharynx, tonsils, parotid and submandibular glands were not included.

In the calculation of the prevalence of malignant tumour account was taken of the follow-up period for each patient. The statistical methods used have been described previously (Einhorn and Jakobson, 1964).

Results

0.6 per cent of the patients developed oral carcinoma during the first year of the diagnosis of leukoplakia, and 1.7 per cent during the first 3 years. Thereafter the cumulative incidence of the oral and lip carcinoma showed a continous increase. 0.2—0.3 per cent of the patients followed up each year developing malignant tumours (Figure). Twenty-five years after the diagnosis the cumulative incidence of oral and lip carcinoma was 7.4 per cent.

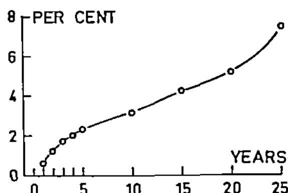


Fig. 1. Cumulative incidence of oral and lip carcinoma in cases of leukoplakia.

TABLE 1

ANNUAL INCIDENCE OF ORAL AND LIP CARCINOMA FOR THE FIRST 5 YEARS AFTER ORAL LEUKOPLAKIA WAS DIAGNOSED

Age	Number of patients	Number of observation-years	Number of cases of carcinoma	*Annual incidence (%)*	
				Present series	Swedish population
20–49	274	1301	2	0.2	0.001
50–69	400	1890	7	0.4	0.01
70–89	109	489	8	1.6	0.03
Total:	783	3680	17		

TABLE 2

ANNUAL INCIDENCE OF ORAL AND LIP CARCINOMA MORE THAN 5 YEARS AFTER ORAL LEUKOPLAKIA WAS DIAGNOSED

Age	Number of observation-years	Number of cases of carcinoma	*Annual incidence (%)*	
			Present series	Swedish population
20–49	995	1	0.1	0.001
50–69	2997	3	0.1	0.01
70–89	1472	7	0.5	0.03
Total:	5464	11	0.20	

The incidence of oral and lip carcinoma with respect to age is given in tables 1 and 2.

Discussion

Since leukoplakia is diagnosed on clinical findings a subjective factor is inevitably involved. As biopsy specimens were taken only on 33 per cent of the series it is difficult to decide what proportion of the cases had carcinoma at the outset. However, as only 0.6 per cent of the patients developed carcinoma during the first year, the overlooking of this disease at the first examination will not have constituted a significant source of error.

From this case series it is evident that the risk of developing carcinoma is particularly great in older patients and during the first years after leukoplakia has been diagnosed. About 8 per cent of the patients aged 70—90 years developed carcinoma of the oral cavity during the first 5 years of the diagnosis. For the patients below 50 years of age the corresponding figure is 1 per cent, and about 0.5 per cent in the subsequent 5-year period. To find whether the observed incidence of malignant tumours of the oral cavity exceeds that ascribable to chance, it is necessary to know the incidence of these tumours in the population group to which the cases of leukoplakia belong, or in a representative control group from this population. No satisfactory control group was available to us, nor to any other author who has reported studies on the incidence of malignant tumours in persons with oral leukoplakia. The Swedish Cancer Registry (Ringertz et al. 1962) was considered to provide the best available basis for comparison. However, as it covers only a small part of the period during which the series of patients were observed, only large differences may be ascribed significance. In comparison with the 1959 Cancer Registry the observed incidence of tumours in the first 5-year period for the various age groups was 40—150 times higher than in the whole Swedish population (Table 1). The incidence observed more than 5 years after the diagnosis was, for the various age groups, 11—100 times greater than for the total Swedish population (Table 2).

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TRAUMATOLOGY OF THE LARYNGEAL REGION

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Etiology symptomatology and management of acute and chronic laryngo-tracheal injuries are outlined and the following conclusions drawn:

1) Patients, who have been exposed t acute laryngo-tracheal trauma ought t be hospitalized for observation, because there is risk for imminent ventilatory insufficiency
2) Immediat therapy in these injuries should not be reduced to routine tracheostomy
3) A definit operation with revision and reconstruction of the airway is more easily done in the acut stage than later on and it is also preferabl from functional point of view
4) During the postoperative period, stents are ery often needed. They must have suitable shape i order t fit well and to giv result which is as anatomically perfect as possible

Of all accidental traumata in the otolaryngologic field, only a small percentage involves the cartilages and soft tissues of the anterior neck. This region is relatively well protected from behind by the spinal column and in front by the protruding cheek and also by the protecting head tilting reflex. Blunt or sharp trauma in this region is however always dangerous. As the narrowest part of the upper respiratory tract is involved there is always a risk of acute or imminent ventilatory distress. In all cases it is important to make a careful preliminary evaluation and an effective action program is necessary with the purpose to preserve satisfactory ventilation, speech and mucous membrane function. Such an approach can reduce the number of chronic laryngo-tracheal stenoses in patients, which now occupy many otolaryngologic beds all over the world for extremely long periods and which very often later on leave the hospitals with a definitive tracheal cannula. The diagnostic and therapeutic procedures which will be outlined in this paper are also applicable in already established chronic laryngo-tracheal stenoses of different origins.

In most textbooks the dynamics of this type of trauma, the symptomatology and the posttraumatic risk factors are cursorily mentioned and clinically too often, the only primary therapy decided for these cases is routine tracheostomy Careful examinations and definitive surgical treatment are as a rule postponed. In the author's opinion the severe acute laryngotracheal injuries should have early definitive treatment — so that secondary infection does not complicate the already damaged tissues. This means that every otolaryngologic department must be prepared with instruments and accessory aids like prefabricated stents, of different kinds for immediate use.

ETIOLOGY

The cause of acute traumatic injuries in this region is — if war injuries are excluded — most often traffic accidents, athletic injuries, manual assaults and

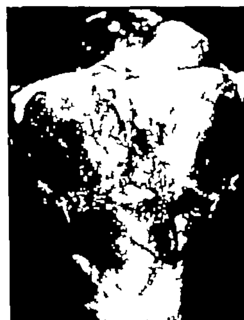


Fig. 1 Typical cricoid fracture in an old patient.





Fig. 2 Preparation demonst rating the great elasticity f laryn in a you g patient. Below with a moderat frontal pressure and above without pressure

strangulation Dependent on the protecting mechanisms mentioned above, especially frontal compressions bring about deleterious injuries on the cartilage skeleton. In old patients fractures in the breakable calcificated cartilages are common (fig 1) In children and adolecents however the cartilages are so elastic, that a moderate compression often results in only soft tissue damage and haemorrage without fractures (fig 2) Closed injuries are sometimes more dangerous than open lacerations. The former are easily overlooked as symptoms often don t occur until several hours after the damage. Therefore, *all patients involving external laryngeal trauma should be hospitalized for observation*

The etiology in different chronic laryngo-tracheal stenoses is listed separately in table 1 Detailed information of this group can be studied in ordinary textbooks and is not dealt with here

TABLE 1

CHRONIC LARYNGO-TRACHEAL STENOSES

Etiology
1 Congenital stridor
2. Conservatively treated traumatic lesions
3. Complications t tracheostomy
4 Postinfection stenoses
5 Tumors. Untreated and sequaelae after surgery and radiologic therap
6 Bilateral vocal-cord paralyses

SYMPTOMATOLOGY

The most common symptoms and their possible mechanism of origin are listed in table 2. Inspiratory stridor is the dominating serious symptom and can be

TABLE 2

ACUTE LARYNGO-TRACHEAL TRAUMA

Symptoms	*Causing factors*
1 Respiratory stridor	Hematoma, fractures, distortion
2 Hemoptysis, coughing	Intratracheal laceration
3. Hematemesis	Oesophageal laceration
4. Hoarseness	Paralyses, oedema, hematoma
5. Swallowing insufficiency	Oedema, hematoma
6. Subcutaneous emphysema	Cutaneous, tracheal or oesophageal laceration
7 Pneumothorax	Via mediastinal emphysema
8 Atelectasis	Aspiration
9 Pain	Fractures, hematoma

caused by distorsion of the arytenoid cartilages and by haematomas and fractures with subluxated fragments. Haemoptysis — eventually initiated or accentuated by coughing — may be a sign of initial aspiration or be due to a mucous membrane lesion. On the other hand haematemesis may follow similar trauma to the oesophagal wall. Hoarseness is a common symptom of vocal cord paralysis,

oedema or haematoma. Pain appears mostly in fractures and is accentuated with swallowing and speaking. Fractures of the hyoid bone and the thyroid cornua are especially painful because they are the site of muscular insertions. Subcutaneous emphysema is a dangerous symptom. The air may be sucked through a skin wound or pressed through a laryngo-tracheal mucosal laceration but oesophagal origin should not be forgotten. *The emphysema is often the result of a preceding inspiratory stridor.* The air may also escape to the mediastinal space and give rise to a pneumothorax. Some of these symptoms are also present in cases of chronic stenosis but here the ventilatory insufficiency and hoarseness are the most dominating problems.

THERAPY

The management of the acute laryngo-tracheal injuries includes:

1. Primary inspection and palpation
2. *Establishment of a free upper airway*
3. Shocktherapy
4. Routine tracheo-oesophagoscopy as well as various X-ray examinations.

The shock in these cases is often due to a true laryngospasm or psychologically to the fear of strangulation. Endotracheal intubation — which is the common initial procedure in nontraumatic ventilatory insufficiency prior to a tracheotomy — is not to be recommended here as it can make the lesion worse and also increase the risk of secondary infection.

If tracheostomy is necessary it has to be performed as far from the lesion as possible and with a minimum of tissue excision. This will make a later reconstruction easier. *It is necessary to conclude that laryngo-tracheal trauma is not viewed properly in the acute phase when therapy is limited to a routine tracheostomy.* The additional examinations include frontal and lateral X-ray projections and also a tomography in order to identify eventual fracture lines and estimate the degree of stenosis. The endoscopic inspections are best performed in a short sapnoe anaesthesia without endotracheal intubation. Praeoperative analyses of the ventilatory capacity is valuable especially in chronic stenosis but not absolutely necessary in acute cases. An approximate quick test regarding the »first second» expiratory and inspiratory volumes during forced ventilation is, however, easily done and gives a rough figure of the degree of stenosis. A valuable further contribution especially praeoperatively in chronic cases are pressureflow determinations across the stenotic part of the upper airway. Intermittent bloodgas analyses are also recommendable.

5. The definitive therapy must be suited to the nature of the injury and to the results obtained by the examinations. There are three different degrees of surgical activity:

A) Endoscopic procedures including instrumental reposition or introduction of stents.

B) Open wound revision and reposition of fragments from outside including drainage of haemorrhage which is very important in order to avoid organisation of haematoma.
C) Acute reconstruction with reposition and skin grafting or resection and end-to-end anastomosis. In these cases an anatomically designed stent may be necessary in order to maintain an adequate lumen.

The acute operative reconstruction is advisable in all severe cases This statement constitutes the third rule in treating these injuries. The number of secondary chronic stenosis can then be reduced the function carefully restored and the hospital stay reduced. The surgical procedures in an actual case are demonstrated in a film which accompanies this general survey on acute laryngeal traumata.[1])

One of the most important factors in reconstructive surgery in larynx and trachea is to maintain or bring about an upper airway with a normal width and configuration This is hardly possible with the aid of cannulas and stents now available and not even with the use of rubber or plastic tubes rough cutted in the last minute. An adequate stent requires the following characteristics: Anatomically correct design, light to wear and made of an indifferent nontoxic and nonallergic material. It must be stiff enough but also a little flexible. A stent with a lumen for speech and ventila



Fig. 3. Laryngo-tracheal cast in place during preparation.

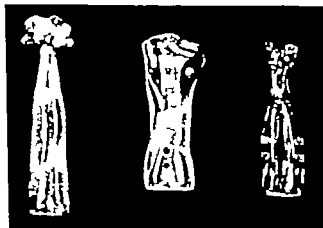


Fig 4. The anatomically configurated stent with its central airway and lateral holes for fixation. Th model t the left includes the whol laryngo-tracheal space. The conical configuration of the subglottic space and its oval cross-sectional area are clearly demonst rated.

) *Laryngo-Tracheal Injuries* Manuscript: N G. Toremalm. Photo: J F Nilsson. Colorfilm, obtainable from the author

tion is preferable to a solid one. It shall be easily fixed in place and also easily removable endoscopically after healing The author has designed an anatomically configurated stent which is built from a cast of normal larynx (fig 3—4) It is available in three sizes.*) The cross-sectional area in the subglottic space is obviously not round as could be expected but has the form of an irregular cone with an oval base (fig 4). This is of great importance and, as a matter of fact, a round tube is unsuitable in this place as it may give either ulcers or have a tendency to slip downwards. Below the subglottis space, however circular stents are usable According to the demands outlined above a flexible and easily retractable spiral stent has been designed and tested (fig 5) *) It is not always necessary to use a stent

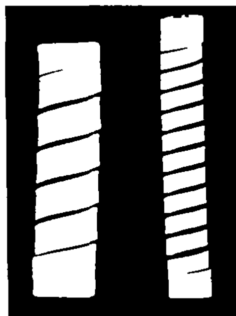


Fig. 5. The flexible Teflon spiral stents for middle tracheal pplication.

but in cases where they are inserted they should be left in place for at least six weeks. Some authors have recommended a more or less permanent use without complications.

In chronic stenosis many secondary problems such as infection, scarring etc. are involved Long periods of observation antibiotic therapy and small operative procedures are common in these cases. Many times, however a well planned and carefully grounded reconstructive operation would have reduced the problems and brought about earlier recovery In small children however it is always wise to observe for a rather long period but it is also necessary to realize that the delay of decanulation can cause great problems educationally and emotionally and also a drawback for the further development and function of the larynx Therefore it is unwise to prolonge the period of observation for more than a year in these cases, without making any attempts to bring about a sufficient ordinary airway by adequate surgery

*) Manufactured by Kifa, Solna, Sweden.

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INTRATRACHEAL TUBE TREATMENT OF STENOSIS OF THE TRACHEA

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Treatment of severe and recurrent cases of tracheal stenosis by permanently implanted tubes of silicone is described.

Severe and recurrent stenosis of the trachea was in three patients treated with permanently inserted silicone-rubber tube in the trachea securing a free and normal respiratory airway

The procedure was the following: after splitting the tracheal wall in the front and removing all scar tissue a silicone-rubber tube of suitable size was placed in the lumen. By a nylon suture passing through the wall of the tube and through the walls of the trachea the tube was fixed to the trachea. — The nylon thread was tied up in front of the trachea at the same time closing the incision in the trachea and the skin was closed without any tracheostomy left (Fig 1).

This procedure enables the patient to breathe normally through the upper airways, to talk and to conduct a absolutely normal life. — The tube seems not to present any obstacle to breathing, coughing or expectoration.

Three patients have now been wearing such intratracheal tubes for more than one year

Case report

1 20-year-old female (Fig. 2). One and half years ago intubated for two days because of unconciousness after veneficium. One week later increasing symptoms of stenosis of the trachea. The stenosis was twice treated with intratracheal dilatators for three months but when the dilatator was removed the stenosis recurred.

15 months ago silicone tube was inserted in the trachea. Since then she has been completely free from respiratory symptoms. Her voice is normal, and she has full-time job as typist.

2. 70 years old male. After severe thoracic trauma with several costal fractures he was treated with artificial ventilation through an endotracheal tracheostomy tube for three weeks. Later on



Fig. 1



Fig. 2.

a tracheal stenosis developed which was two times operated on with intatracheal dilatator for three months.

When the stenosis recurred for the third time a silicone-rubber tube was inserted 15 month ago. He is now free from respiratory symptoms, talks, breathes and coughs normally and is ble to do some lighter work.

3. 73-year-old male. Five years ago tracheostomy in connection with prostatectomy. Since then slowly increasing respiratory troubles and coughing. 12 months ago increasing symptoms of tracheostenosis. The tracheal wall was completely weak. A silicone tube was inserted in the trachea. Since then no inspiratory troubles and especially no difficulties in expectoration. H later had a herniotomy and stood the anaesthesia well.

It is of course with some hesitation that one makes such an intratracheal implantation without tracheostomy and the patient must of course be watched very carefully the following days. It is however our experience that they patients have by far lesser trouble postoperatively than following a tracheostomy proper and we did not observe any difficulties neither in respiration nor expectoration.

In all three patients the upper part of the tube is to be seen with a larynx mirror. It's lumen is free and no stagnation of mucus is evident.

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POSSIBILITIES IN THE TREATMENT OF SEVERE LARYNGEAL DAMAGE

Herman Diamant

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At our department we hav had two cases with extensive traumatic lesions of the larynx during the last years. Both cases were very complicated by rib fractures and lung complications. A female involved in car-accident showed t the first examination n air-passage through th glottis. Everything was don to restore an airway Still three years after the trauma the patient can not breathe properly She denies further treatment.

The ther case concerns man, 23, involved in a tractor accident. The larynx and the thorax were brushed. He got several rib fractures and a difficult shock which stopped immediat operation. Three weeks after th accident we start d the restoring measures. There was no success, however until w used nylon-tube. After two months in place and after a laterofixation on one side, the result is excellent and the patient is in full work.

Despite the comparatively protected situation of the larynx, laryngeal damage is not very unusual. But even for large materials comprising accidents it is difficult to determine the frequency Treatment is often rendered more difficult on account of the comminute character of the damage, i.e. the patients frequently suffer from several traumatic injuries. Combination with fracture of the lower jaw is met with rather often. There is general agreement, as is evident from the comprehensive article by Ogura & Roper Surgical correction of traumatic stenosis of larynx and pharynx, (1959), that it is necessary to perform an acute operation, comprising as a rule the direct reposition of the laryngeal cartilage. There are cases, however where it is necessary to wait for a considerable time before operating, since acute operation may have to be postponed on account of other injuries. The laryngeal damage will then have a more chronic course than was expected from the outset

The three cases reported on here illustrate these different possibilities. The first was a girl, aged 18 years, who as a result of a motor-car accident, sustained deep contusions in the face, left-sided pneumothorax, and fracture of the larynx. On account of her poor general condition and the rather severe concussion of the brain she had sustained, intubation was immediately applied. It proved very difficult, however to maintain the air-passage via the tube. Tracheotomy had to be per formed almost at once. Repeated efforts were made to insert a rubber tube from above Finally this proved successful. It was intended to let the tube [illegible] but as so often happens with rubber tubes, the secretion around the tube [illegible] evil-smelling and surrounding tissues showed all the signs of grave infe[illegible] the trachea After about 5 weeks the patient was transferred to the [illegible] of Thoracic surgery at Karolinska sjukhuset, where laryngofissure was [illegible] and a teflon prosthesis was inserted. This was kept in place for a [illegible] time. Altogether she was treated for about one year with the prosth[illegible] she obtained quite a fair air passage, but several check-ups [illegible]

respiratory passage was far from sufficient Retraining was not successful, and she was either unable or unwilling to work.

Subsequently on mental grounds, and for technical reasons connected with Insurance, the patient did not wish to continue the treatment despite her rather poor spirometric values. She has now five years after the trauma, a very hoarse voice as well as a crooked and quite narrow air passage as a result of her injuries.

The second patient was a man, aged 21 years, who, when loading a lorry received a hard blow on the larynx. This caused a very severe fracture of the larynx. Moreover the blow resulted in bilateral pneumothorax with pronounced mediastinal emphysema. He was immediately tracheotomized and low-pressure drainage was applied on the left side. The patient showed signs of anoxic damage, which however soon disappeared. At the first operation, which was postponed for 14 days on account of the patient's condition, it was possible to reveal a fracture of the larynx, where, in the first place, the arytenoid cartilage was damaged in the vicinity of the opening into the larynx. The thyroid cartilage was also fractured, and it was difficult to obtain an adequate air passage. In consultation with Ass. prof. Carlens at the Department of Thoracic surgery treatment was undertaken at Karolinska sjukhuset. A teflon prosthesis was inserted and then allowed to remain for about 3 months. It was changed from above with a high degree of success, but when finally removed it was found that there was still an extensive development of granulation.

Consequently it was decided to perform a laryngofissure and to remove all tissue, to keep a laryngostoma open and to subject the granulations to intense treatment so as to obtain a passage. Instead of a teflon prosthesis a polyethylen tube was inserted which was taken from a disposable syringe. The syringe was cut to shape and fixed with steel wire through the skin. The tube was changed several times, and gradually the air passage became so satisfactory that the tube in the trachea could be removed. However the patient did not have a good respiratory passage because of bilateral posterior paralysis, which had apparently occurred in connection with the trauma and which could not be observed previously on account of the swelling Laterofixation of the right vocal cord was carried out which was fixed far out. As a result of this procedure the patient's air passage was quite satisfactory The lung-function test showed only a slight reduction in functional capacity The results can be regarded as very satisfactory Naturally the patient's voice is hoarse, but he has resumed work, which he is able to attend to without difficulty Repeated check-ups have shown that his condition is quite stationary

The third case, which occurred quite recently was a man, aged 25 years, who as a consequence of a motor-car accident, sustained four defined injuries. 1) Severe contusion of larynx, 2) mandibular fracture of both colla mandibulae and of the left corpus 3) fracture of the vertebra C2, and 4) ulnar fracture in the right forearm.

Despite these injuries the patient was able to reach the nearest house two kilometers away from which the call for assistance was sent. As soon as he reached hospital tracheotomy was performed. The patient was put in an extension bed on account of his vertebral injury He had then only slight neurological symptoms.

Already after a few days it was decided in spite of the patient s rather troublesome, immobile condition, to provide for both the laryngeal damage and the fracture of the lower jaw! It was possible to fix the lower jaw in what seemed to be a satisfactory position. A ventricular feeding tube was inserted and it was possible to concentrate on the laryngeal damage. The left thyroid cartilage was completely crushed, so that it could not be restored. The arytenoid cartilage could not be found, and the region of the left vocal cord was completely lacerated There was no possibility of covering the defect with mucous membrane. The right side was more or less intact. The cricoid cartilage appeared to be intact at the first investigation. In view of the existing conditions one had to restrict oneself to restoring as far as possible, the air passage and to leaving quite a large laryngostoma. A plastic tube, made from a 5 cc disposable syringe, was inserted. A satisfactory air passage was obtained, but the entire introitus was very swollen. How ever both the epiglottis and the arytenoid cartilage on the right side seemed to be normal. The tube was changed after 14 days and the air passage appeared then to be very good. At this second operation fracture of cartilago cricoidea was established. This was split and the new plastic tube was introduced into the trachea near the tracheostomy tube.

At the next stage the tracheostoma was made further down. Granulations were substantially reduced, and the air passage was becoming stabilized. Treatment is in progress.

On the basis of these three cases I wish to state that, in my opinion, it is of course desirable to operate patients, suffering from laryngeal damage, as soon as possible. It is not so easy however to get all the cartilaginous parts in position when the fractures are very severe. Consequently I believe, especially in cases where there are comminute fractures, that attempts should rather be made to restore the air passage in such a way as to provide a good starting-point for further procedure.

The third case affords a good illustration of how complicated these cases can be. Not least of all vertebral fractures imply a serious disadvantage in the treatment of laryngeal fractures.

It may be stated in short that there is no reason to abandon hope even if the first operation has to be performed at a comparatively late stage.

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ÜBER DIE BEHANDLUNG DER LARYNX- UND TRACHEAVERLETZUNGEN

Aus der Univ.-Ohrenklinik, Turku (Vorstand: Prof. Otto H. Meurman)

Otto H. Meurman

Turku, Finnland

Es werden 3 Fälle mit Larynx- und Tracheaverletzungen beschrieben. 2 Patienten mit einem posttraumatischen stenosierenden Prozess in Larynx und Trachea konnten durch eine Dauertubusbehandlung geheilt werden. Bei dem dritten Patienten konnte eine völlig zerrissene Trachea durch primäre Naht ohne Stenosierung wiederhergestellt werden.

Durch ihre Struktur und Lage sind der Kehlkopf und die Luftröhre verhältnismässig gut gegen äussere Gewalt geschützt. Andererseits verursachen wieder die schweren Traumata, die diese Organe treffen, leicht stenosierende Prozesse, deren Behandlung meistens schwer und langwierig ist.

Wir haben während der 4 letzten Jahre 3 solche schwere Fälle gesehen, über die kurz berichtet werden soll.

Fall 1. Eine 18-jährige Frau. Nach Uneinigkeiten in der Familie sprang die Patientin vom 4. Stock auf eine Steinstrasse und erlitt u.a. eine Gehirnerschütterung, Kieferfrakturen und zahlreiche Gliedfrakturen. Es ist ein Wunder, dass sie überhaupt am Leben blieb. Einige Stunden nach dem Ereignis bekam sie erhebliche Atembeschwerden und ein Emphysem am Hals, weshalb eine Nottracheotomie durchgeführt werden musste. Als die Patientin später in die Ohrenklinik zur Behandlung kam, stellte man fest, dass der untere Teil des Larynx unterhalb der Stimmlippen und der obere Teil der Trachea bis zum Tracheostoma ungefähr in einer Länge von 2—3 cm total obliteriert und durch Granulation ausgefüllt war.



Bild. 1



Bild. 2.

Bild 1. Der Tubus oberhalb des Tracheostomas.
Bild 2. Die Ende der Trachealkanüle in dem Tubus.

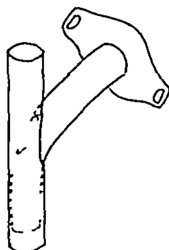




Bild 3. Bild 4

Bild 3. Ventilkanüle und Tubus.
Bild 4. Fall 1. 2 Jahre nach dem Dekanülement.

In einer Operation, durchgeführt von aussen, konnte man weiter feststellen, dass der Vorderbogen des Ringknorpels völlig gebrochen war. Möglicherweise war die Verletzung durch das starke Vornschleudern des Kopfes beim Aufprall zustandegekommen. Die Granulationen wurden entfernt und oberhalb des Tracheostomas auf das obliterierte Gebiet wurde ein Portex-tubus (Polyvinyl Chlorid) eingelegt, der im Bereich des Tracheostomas fixiert wurde (Bild 1). Der Tubus war auf diese Weise nur schwer in der richtigen Lage zu halten. Ausserdem irritierten die Fäden das Tracheostoma. Deshalb gingen wir zur folgenden Methode über: Der Portex Tubus wurde nach unten verlängert, in die Vorderwand in der Höhe des Tracheostomas ein Loch geschnitten und durch dieses die Trachealkanüle hineingesteckt (Bild 2). Auf diese Weise war die Fixierung fest. Das Tracheostoma beruhigte sich bald und keine Granulation bildete sich mehr im Lumen der Trachea und des Larynx. Der Tubus wurde in Abständen von einigen Wochen in direkter Laryngoskopie entfernt und die Situation beobachtet. Wegen Stenosierung im Ringknorpelgegend musste man ihn immer wieder hineinsetzen. Um der Patientin das Sprechen zu erleichtern, wurde die gewöhnliche Kanüle durch eine Ventilkanüle ersetzt (Bild 3). Damit konnte die Patientin ohne Schwierigkeiten sowohl atmen als auch sprechen. Insgesamt blieb der Tubus für etwa ein Jahr liegen. Während dieser Zeit konnte die Patientin ein normales Leben führen. Das Dekanülement bot keine Schwierigkeiten und den heutigen Zustand, 2 Jahre nach dem Dekanülement zeigt das folgende Bild (Bild 4). Im oberen Teil der Trachea ist eine kleine Verengung zu sehen, die sie jedoch nicht hindert frei zu atmen.





Bild. 5, Bild. 6.

Bild 5. Fall 2. ein Jahr nach dem Dekanülement.
Bild 6. Fall 3. drei Monate nach dem Dekanülement.

Fall 2 R F Ein 10 jähriger Ladengehilfe. In Geistesverwirrung versuchte er sich zu erhängen Der Strick riss jedoch und der Junge lief auf die Strasse und versuchte sich unter ein Auto zu werfen. Es gelang jedoch dem Autofahrer rechtzeitig zu bremsen und der Patient wurde ins Krankenhaus gebracht, wo sich nach einer Weile ein starkes Ödem an Hals und Gesicht entwickelte. Gleichzeitig traten Atembeschwerden auf. Es musste eine Nottracheotomie vorgenommen werden Später wurde der Patient in die Ohrenklinik verlegt. Hier wurde festgestellt, dass der Strick den oberen Trachealabschnitt dicht unter dem Ringknorpel völlig durchtrennt hatte. Der Ringknorpel war stark nach oben verlagert. Der Schleimhautdefekt im Verletzungsbereich war ziemlich gross. Es bestand eine beiderseitige Recurrensparese. Es war in dieser Phase nicht mehr möglich die Trachea zu suturieren Um eine schnellere Epithelisierung zu erzielen, wurde ein Hautlappen von Hals in Defekt eingenäht und ein Portex Tubus eingelegt. Als die Haut gut eingewachsen war wurde das Laryngotracheostoma geschlossen und der Portextubus mit der Kanüle fixiert, wie auch bei dem ersten Patienten. Die Recurrensparese auf der rechten Seite bildete sich allmählich zurück und das Dekanülement und die Entfernung des Tubus konnten endgültig nach einem Jahr vorgenommen werden. Auch in diesem Falle war der Patient mit Kanüle und Tubus arbeitsfähig. Abbildung 5 zeigt den Zustand der Trachea ein Jahr nach dem Dekanülement.

Fall 3 V R. Ein 45 jähriger Arbeiter Bei der Arbeit im Hafen schlug ein schwerer Papierballen dem Patienten gegen den Rücken, wobei der Patient zwischen Ballen und einer Wand gepresst wurde. In einer halben Stunde entstand ein kräf

tiges Emphysem am Hals und Atembeschwerden traten auf. Bei der Untersuchung stellte man fest, dass die Schleimhaut des Larynx stark gerötet und geschwollen war. Das Lumen war durch blutigen Schleim verlegt. Die Epiglottis war ungefähr in der Mittellinie gerissen. Recurrensparese auf der linken Seite. Wegen zunehmender Atembeschwerden wurde die Trachea freigelegt. Dabei stellte man fest, dass die Trachea zerrissen war unterhalb des 3. Knorpelringes. Der untere Trachealrand hatte sich in das stark gequetschte Mediastinum hineinretrahiert. Die beiden Recurrensnerven konnte man in der gequetschten Weichteilen erkennen. Es gelang die Trachealwundränder durch Naht wiederzuvereinigen. Die Trachea heilte gut und das Dekanülement konnte 2 Wochen später vorgenommen werden. Inzwischen sind 3 Monate vergangen. Die Rekurrensparese auf der linken Seite ist unverändert. Abbild 6 zeigt ein Tomogramm aus dem Verletzungsbereich. Die Veränderungen sind geringfügig.

Diese Fälle zeigen die Schwierigkeiten, die bei Larynx- und Tracheaverletzungen vorkommen können. Wenn ein Trachealriss relativ bald vernäht werden kann, ist das Resultat gut und die Behandlungszeit nicht sehr lang. Bei stenosierenden Larynx- und Tracheaverletzungen kann man mit einer verhältnismässig konservativen Dauertubusbehandlung, die den Patienten nur wenig beeinträchtigt, gute Resultate erzielen.

Summary

Three cases of severe traumatic larynx and trachea disorders are presented. Two of these were succesfully treated with a permanent Portex (Polyvinyl Chlorid) tube. In the third case the trachea could be primarily sutured.

Kaskenk. 3 C. Turku,
Finnland

THE ACUTE TREATMENT OF LARYNGEAL INJURIES

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Aspects on traumat logy of the larynx are discussed in connection with a current case. Reconstruction of cricoid and thyroid cartilage and mucous membrane was done immediately after the trauma. Result and methods are discussed.

Although a constantly increasing number of severe injuries to the head ar neck reach our emergency departments every day those involving the larynx ar trachea are few This means that the clinical experience in treatment of injuri indicates, however that early diagnosis and treatment of these injuries are outmost importance for successful results. (1—4)

In relation to the present discussion it seems to be worth while mentioning case treated in our clinic recently

A thirty four years old policeman drove during a heavy snowfall behind a c which suddenly turned to the right avoiding a truck loaded with wood. The polic man hit the truck and the wood came into his car and struck him on the hea and the throat. He was brought to a country-side hospital where a rubber tube w introduced through the open wound on the throat into the trachea. Twelve hou later the patient arrived into our clinic. He had a severe concussion and becau of suspected haematoma of the brain a craniotomy was made. Thereafter th larynx was explored.

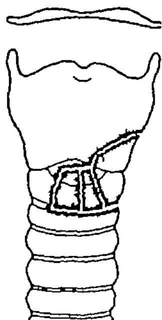


Fig. 1 Schematic drawing of the damage of the larynx in the presented case.

An open eight centimeter long wound was found across the throat. A low tracheotomy was performed and the larynx explored. The cricoid cartilage was crushed into four fragments. (Fig. 1) The cricothyroid membrane was lacerated, a part of the left side of the thyroid cartilage was torn off from the rest and the mucosa of the larynx was lacerated apart from a small area on the posterior wall. The mucosa of the larynx was sutured with catgut. The fragments of the cricoid and thyroid cartilage were sutured in place with nylon sutures and a good adaptation was achieved with stable support by the laryngeal sceleton.

One month after the accident the patient was in good enough condition to leave the respirator and direct laryngoscopy showed only a slight swelling of the musoca of the posterior wall of the subglottic space. The left vocal cord was paralysed due to the severe damage of the left side of the larynx and the left recurrent nerve. The patient was given antibiotics two weeks after the operation to prevent chondritis as the operation was performed twelve hours after the accident. No signs of postoperative infection occurred[1]) Four months after the operation no complications have appeared.

Earliest possible treatment of tracheal injuries with preservation of the damaged cartilage, careful adaption when possible and suture with nylon seem to be essential for good results. According to my opinion a stent should be used only when adequate cartilage support cannot be achieved by the tracheal sutures. Antibiotic treatment should be given during two weeks after the operation to prevent postoperative chondritis.

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[1]) Tracheoscopy fourteen months after the accident shows the same picture as after four months with normal laryngeal and tracheal wall apart from 4 mm thick bulging of the mucosa 2 cm subglottic on the left side (April 1967).

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TRACHEAL CHANGES AFTER TRACHEOSTOMY

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Tracheal stenosis is a rare but serious complication of tracheostomy The frequency of manifest stenosis with interference of respiratory function was 2% in 250 surviving cases of tracheostomy at our hospital 1960—1961 In order t investigate if minor degree of stenosis develope after tracheostomy without being noticed X-ray examination has been done on patients who have had tracheostomy at the hospital during 1965 The results are given and discussed.

Tracheostomy possibly with subsequent respirator care, has become an all more common treatment in the big hospitals As an example it can be mentioned that, in the ear clinic, Regionsjukhuset Örebro in 1955 there were 31 tracheostomies carried out, while in 1965 the number was up to 132. Thereby the number of complications after the operation has also been greater Amongst the complications, one of the most serious is tracheal stenosis. In the literature so far there are only a few reports on this complication Binet and Aboulker (1961) gave an account of a material from Hopital Claude-Bernard of 520 tracheostomies where 120 were re-examined and 18 cases of stenosis were found. A later work from the same hospital is a continued study of a larger material. Of 912 cases who were operated for tracheostomy 417 were controlled and 36 cases of stenosis were found, i.e. 8% of the controlled group (table 1) In connection with treatment by antibiotics and even corticosteroids, the changes have regressed in 15 of the cases. Amongst the remaining 21 cases, 4 have died from complications to the stenosis, 3 patients have become permanent cannula cases, while finally the rest were successfully operated upon The so-called supra-orificial stenosis i e. stenosis in the cricoid region above the tracheostomy have all been operated with good result, while the sub-orificial stenosis according to the author were surgically difficult to treat, therefore in these cases a permanent tube was suggested Durcan (1963) and Binns (1964) gave a report of one case each of tracheal stenosis, which with good result was treated conservatively i e. with antibiotics, corticosteroids and in Durcan s case dilatation. Hoffman (1963) has studied how is not given, a material from a thoracic surgical clinic comprising 168 cases where scar-stenosis occurred in 5—10%. In the large monography over complications of tracheostomy by von Schulthess (1964) there is no analysis of the material with regard to existing tracheal stenosis.

With the intention of studying the frequency of tracheal stenosis and if possible finding the background to the origin of the stenosis, a tracheostomy material from the Regionsjukhuset in Örebro has been analysed. It concerns 447 cases of tracheostomy during the year 1960—1961 Amongst 259 surviving and with the tube removed, are 4 with manifest stenosis accompanied by respiratory insufficiency (table 1). In all cases the patients were over 50 years of age and had been treated in a respirator from 8 days to 6 weeks During the period of tracheostomy and respirator care in all cases special difficulties occurred e.g

TABLE 1

FREQUENCY OF TRACHEAL STENOSIS FOLLOWING TRACHEOSTOMY

Author	No. of cases with tracheostomy	No. of cases studied	No. of cases with stenosis
Binet o. Aulker (1961)	520	120	18
Mollaret et al. (1962)	912	447	36 (21)
Hoffman (1963)	168		5—10%
Ekedahl et al. (1965)	447	259	4 (4)

No. in brackets = fibrous stenosis.

TABLE 2

Case no.	Basic illness	Complication during tracheostomy operation	Durat. of tracheostomy Complic. dur that time	Durat. of respirator treatment	Rise of stenosis symptoms after rem. of tube.
010921 H. A.	Fract. ribs V—IX, pneumothorax, haematothorax	At thoracotomy difficulty dur change from M gill tube to tracheal cannula	10 days Delirium	8 days	About 1 yr
070705 R. L.	Polyradiculitis (Breathing paralysis)	Uncomplicated	10 weeks Blood pressure incr causing anxiety Frequent tube changes because of leakage	8 weeks	6 weeks
950821 K. O	Cardiosclerosis, Rheumatoid arthritis, Prostata hyperpl Bronchopneumonia	Uncomplicated Cannula changed after 2 hours	4 weeks Repeated haem. in tracheostoma	2 ½ weeks	1 ½ years
971013 S. A.	Infarctus cordis	Uncomplicated	5 weeks Fever and much secretion	5 weeks	5 weeks

delirium, frequent tube changes, high pressure in the cuff caused by bleeding from the tracheostomy and plentiful secretion with frequent suckings. The stenosis symptoms have in all cases shown themselves a fairly long time after the tube was removed i.e. from 5 weeks to eighteen months (table 2) The site of the stenosis is at the heigh of the tracheostomy or below this i.e. orificial or suborificial according to the nomenclature of Aboulker and Sterkers (1961). The stenosis has been fibrous in character without any spontaneous tendency to regression. In two of the cases tracheoplasty has been tried, but with poor results and both have permanent tracheostomy In the third case there are contraindications for operation and the fourth has died from heart rupture.

In going through the related material we have started from the records. One could suppose, that further cases of stenosis with less pronounced symptoms are available. In order to investigate this and at the same time see how often tracheal changes appear after tracheostomy with or without respirator care, we have called all the survivors of those who underwent tracheostomy in 1965. The total number of tracheostomies was 132 and of these 79 died before and 2 a short time after the

tube was removed, all from the basic illness and not as a complication of tracheostomy Four cases are still tracheostomised and six have not been re-examined for various causes. There remain consequently 41 cases (table 3)

TABLE 3

Total number of cases with tracheostomy	132
Dead	81
Still with tracheostoma	4
Examined	41
Not examined	6

The investigation has implied X-ray examination in 2 planes and in a number of cases tracheoscopy also In 21 cases there were no visible roentgenologic changes in the trachea while 16 cases showed smaller changes diverging from normal material and which therefore according to roentgenologist can be ascribed to tracheostomy In 3 cases there was a clear restriction of the lumen. Two of the cases are older patients, a 60 year old woman and a 61 year old man, both of whom are treated, because of breathing insufficiency with tracheostomy and respirator the one during 14 days and the other during 15 days. The roentgen control showed stenosis of the trachea with impression of the front wall and the right side level with the tracheostoma in the one case and in the other a narrowing from both sides. Tracheoscopy showed in both cases, a narrowing from side to side and in the second case also a granulation polyp on the front wall. In both cases the narrowing of the lumen amounts to a fifth of the width of the trachea. Common to both these two cases is that they are invalids, the one through severe multiple sclerosis and the other through an advanced carcinoma of the oesophagus, which means that both are for the most part bed-ridden and without greater demands on the respiratory apparatus. The third case is a 3 year old girl, who was tracheostomised on account of pseudo-croup Clinically the following period was normal but roentgen control 4 months after removal of the tube showed a narrowing of the trachea from the front at the site of the earlier tracheostomy Tracheoscopy revealed a little polyp which in later examinations has shown a tendency to diminish.

A further case of stenosis appears in the 1965 material, but here the change is revealed already in connection with removal of the tube. It concerns a 60 year old woman, who was treated with a respirator through a tracheostomy for 13 days. In an attempt to remove the tube 2 days after the respirator treatment was finished the patient got obvious breathing difficulties and the trachea was shown to be nearly wholly obliterated by granulations level with the tracheostomy which was again opened up Antibiotics and corticosteroids were given for three weeks, after which the tube could be removed without difficulty It has however shown roentgenologically as well as by tracheoscopy that a clear narrowing of the lumen to barely a pencil width is present, but the narrowing is soft and one can without difficulty pass a bronchoscope. We have extended the steroid and antibiotic treatment further and got a certain regression, but clear stenosis remains,

however not of a fibrous type. A moderate degree of respiration insufficiency is present.

Apart from the 3 year old girl, one finds in all the 7 cases of stenosis certain common factors, which must be considered to have etiologic importance. All are over 55 years old and have been treated in a respirator via tracheostomy In 5 of the cases special difficulties have appeared during this period of care. In order to investigate which changes appear acute in connection with tracheostomy and respirator care, we have examined the trachea of those cases who have died under such treatment In all cases we have found very serious changes, macro- as well as microscopic. One finds ulcerations of the mucous membrane, which within fairly large areas go right down to the tracheal cartilage especially within that region, which is exposed to the pressure of the cuff. Changes are found however even level in height with the point of the cannula.

In the large material which is accounted for from Hopital Claude-Bernard, about half the cases of stenosis are caused by high tracheostomy which as known earlier is considered to be the most common cause of tracheal stenosis.

In our material, and to a certain degree also in the French, stenosis was found in spite of tracheostomy correctly performed, a stenosis which was situated at the level of the tracheostomy or lower down. Aboulker and his cooperators state that a cuffed cannula carries a risk of stenosis. It is quite clear from our investigation, that the pressure, exerted by the cuff on the mucous membrane of the trachea causes serious changes in the latter which can lead to secondary stenoses with grave consequences. Accordingly one should pay great regard to this and as often as possible relieve the pressure in the cuff thus giving the mucous membrane periods of full circulation so that the necroses are prevented. In severe cases of manifest, fibrous stenosis, a fairly long interval has occurred between removal of the tube and the clinical symptoms of stenosis. It is perhaps possible to prevent the appearance of fibrous scar stenoses by treatment during the healing period, of the grave tracheal changes which we have seen in the postmortem material. All respirator-treated patients should, according to our opinion, about one week after removal of the tube, undergo roentgen examination of the trachea and tracheoscopy Treatment with antibiotics and possibly corticosteroids are indicated in those cases, where one finds a tendency to stenoses.

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DISCUSSION

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At the Oto-laryngological department of Rikshospitalet Oslo, a diagnostic and therapeutic scheme is followed in cases of traumatic lesions of the larynx and the trachea

Examinations	Clinical	
	Radiologic	
	Endoscopic	
Surgery	Tracheostomy	
	Exploration	Larynx
	Reconstruction	Trachea
		Recurrent nerve
		Additional structures and organs of the neck

I want to draw your attention in particular t the recurrent nerve in cases of tracheal injuries. It has to be especially explored and repaired in order to establish the most f vourable conditions for its regeneration.

I would also like to emphasize the importance of adequate examination and treatment of the injury as early as possible. Three cases of complet transversal rupture of the trachea and both recurrent nerves have recently been admitted to our department In two of these cases the accident had taken place 3 months before treatment In these cases the results were disappointing among other things due to extensive scar formation. In the third case repair was performed of the day of injury and the results including laryngeal function were satisfactory

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As a comment to dr Toremalm s laryngeal prothesis moulded fter the normal larynx, I shall present a case treated at *Rikshospitalet, Oslo, in 1917*

The patient a male had 7 years before sustained a severe trauma against his larynx. He rapidly developed a laryngeal stenosis, and different types of treatment, including laryngofissure, excision and electrocoagulation of scar tissue were unsuccessful. When admitted to the hospital this time, the patient was still dependent on his tracheal cannula.



Protheses for dilatation of larynx

It was now decided to try dilatation protheses. These were formed after moulds from a human larynx, and were made in a small and a large size. As material was chosen acryl, which at that time was a new inert material. Under local anesthesia, and after excision of scar tissue, the small prothesis was inserted in the larynx. After 14 days it was exchanged for the large prothesis, which was worn almost 3 weeks. The passage through his larynx was now so wide that the tracheal cannula could be removed permanently

I have been in regular contact with th patient through the 19 years which have passed since then. His voice is slightly hoarse, but he does not feel any discomfort from his laryngeal stenosis not even during muscular exercise

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PRINCIPLES IN THE ANATOMIC ORGANIZATION OF THE VESTIBULAR NUCLEI AS DEMONSTRATED IN GOLGI AND EXPERIMENTAL STUDIES IN THE CAT

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Th present account was centered around recent studies on the vestibular nuclear complex and was particularly concerned with aspects of the fiber anatomy assumed to be of interest in an analysis of the functional organization. Experimental investigations have shown that the various efferent fiber connections have their particular and often restricted sites f origin. A similar principle is valid for the afferent connections. Regional cytoarchitectural variations are revealed, corresponding largely with the differences in fiber connections. Integration of vestibular impulses with those from ther sources is assumed to take place in these nuclei. Interest was therefore devoted to observations on interconnections between the subgroups f the complex by way of axons and collaterals as well as dendrites; the presence of internuncial cells; and the synaptic relations between afferent fibres and the nerve cells. Related findings made in Golgi study by the uthor were referred. A correlation of some anatomical and physiological observations was made.

For detailed surveys nd discussions on the present knowledge f the anatomic and functional organization of the vestibular nuclear complex, the reader is referred to the following publications:

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MODERN DIAGNOSTIC METHODS IN OTO-NEUROLOGY

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In the University E.N T Clinic, Rigshospitalet, Copenhagen we have since 1950 been extending otoneurological investigations t comprise also nerves other than the eighth one, which are anatomically closely related to our usual field, i.e the first, fifth, seventh, ninth, tenth, eleventh, and twelfth nerves.

Testing of the named cranial nerves is, very naturally done by the otorhinolaryngologist who i used to evaluat the local appearances in the nasal cavity pharynx, larynx, and oral cavity This obviates erroneous assessments due to local diseases of no significance to the intracranial local diagnosis.

As far as the first cranial nerve is concerned. Determination of threshold values and fatigue and the significance of these tests to intracranial local diagnosis. More over tests for distinguishing real from non-real hyposmia are mentioned.

In respect to the fifth and seventh cranial nerves: Quantitative sensibility in the trigeminal area, quantitative investigation of the nasolacrimal reflex, quantitative test of taste, and test of stapedial function and the application of these tests in intracranial local diagnosis.

Through many years we have had occasion t examine all patients admitted t the neurosurgical department with a suspicion of intracranial disease This has given us an opportunity of comparing the results of the otoneurological investigations with the pathological changes found at operation.

In accordance with the abstract we shall first proceed to the testing of the sense of smell

By rhinoscopy we ascertain whether there is free access to the olfactory regions, and we assess the appearance of the mucous membrane.

Thereafter a preliminary test is done with 8 known odorous substances, including musk, coffee, and phenylethyl alcohol which are pure olfactory stimulants i.e they affect only the sense of smell, while the others, benzaldehyde, citral menthol, turpentine, and benzine are mixed olfactory trigeminal stimulants, i e. they affect, apart from the sense of smell, also the peripheral end organs of the trigeminal nerve in the nasal mucosa

The patient is asked to sniff the test substance, first into one and then into the other nasal cavity with the same force and to state whether the smell in both sides is the same and whether he can recognize the substance.

Thereafter a quantitative test is done with Elsberg s olfactometer

The principle of this method is to blow an air mixture saturated with the smell concerned towards the olfactory region during apnoea. As shown in Fig 1 the apparatus consists of a cylindrical bottle with a volume of 500 ml. At the top the bottle is closed with a tight-fitting rubber stopper through which 2 class tubes pass, one ending about 1 cm above the odorous substance and the other a couple of cm beneath the stopper Superiorly both glass tubes are connected airtight with fairly

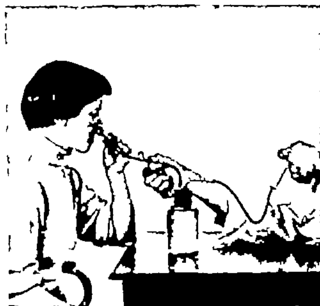


Fig. 1. Procedure in determining Minimum Perceptible Odor (M.P O)

thick walled rubber tubes. At the end of the rubber tube which is connected with the short glass tube there is a nose piece of suitable size, so that it can fit the walls the nostril snugly At the middle of this rubber tube there is a pinch cock by which the lumen of the rubber tube may be opened with a quick movement. If the rubber tube is of suitable thickness and of sufficient elasticity the opening will be instantaneous.

The other rubber tube is connected with an airtight Luer glass syringe of 30 ml with graduation marks for every ml.

1 ml air is sucked into the glass syringe which is then connected with the olfactometer The patient places the nose piece into one nostril with the opening pointing to the olfactory region (and this must be carefully checked each time) and holds his breath. The air from the syringe is injected into the olfactometer the pinch cock is opened with a quick movement. Now a corresponding odour saturated quantity of air which has been injected into the bottle is blown towards the olfactory region. As soon as this has been done, the nose piece is removed, and the patient is to state whether he can smell anything at the very moment that the pinch cock is opened Later perceptions of smell, and doubtful responses, are recorded as negative. At the end of half a minute the same procedure is repeated on the contralateral side, and this is then continued alternately on the right and left, increasing the quantity by 1 ml every half minute until the patient states that he can smell the substance This gives the threshold value in ml, i.e. a relative measure.

Elsberg used the minimum identifiable odour (M.I O), while we use the minimum perceptible odour (M.P O), as the recognition of the various odorous substances depends upon the patient s previous experience If he does not know the substance it is impossible to fix a M I O., while the M.P O can always be fixed.

TABLE 1

THRESHOLD VALUES FOR COFFEE IN DIFFERENT AGE GROUPS

Age:	14–20		21–30		31–40		41–50		51–60		61–70		71–80		>80		Total No. in the groups	
M.P O ml.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.
2	2		2	4	1	1											5	5
3–4	3	5	13	12	7	7	4	4	5	5	1	2					33	35
5–6	1	2	8	6	6	5	4	5	4	3	2	4	3	2	1	1	29	28
7–8	1		2	3	3	3	3	2	2	3	1	1	1	2			13	14
9–10			1	1		1			1	1	2	1	1	1			5	5
11–12							1	1			4	1					5	2
13–14												1		1		1	0	3
15–16													1				1	0
17–20															1		1	0
21–25																	0	0
26–30																	0	0
>30									1	1	3	3	3	3	1	1	8	8
No. of pts.	7	7	26	26	17	17	12	12	13	13	13	13	9	9	3	3	100	100

TABLE 2

THRESHOLD VALUES FOR CITRAL IN DIFFERENT AGE GROUPS

Age:	14–20		21–30		31–40		41–50		51–60		61–70		71–80		>80		Total No. in the groups	
M.P O ml.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.
2	2		5	2			1	1						1			8	4
3–4	3	5	10	12	8	7	2	1	2	4	2	3	3	2			30	34
5–6	1	1	7	8	5	6	4	5	7	5	1	2		1		2	25	30
7–8	1	1	4	3	2	2	1	1	2	1	2	1	2	1	1		15	10
9–10				1	1		4	3	1	2	2	1			1		9	7
11–12					1	2		1			1	1					2	4
13–14											1						1	0
15–16															1	1	1	1
17–20											1	1					1	1
21–25																	0	0
26–30												1					0	1
>30									1	1	3	3	4	4			8	8
No. of pts.	7	7	26	26	17	17	12	12	13	13	13	13	9	9	3	3	100	100

Table 1 presents tests of M.P O for coffee on 100 normal subjects of all ages and Table 2 the M.P O for citral on the same 100 persons.

It may be seen from the results that the sense of smell decreases with advancing age (presbyosmia) as has been demonstrated previously

In this connection it is of more interest that differences in threshold values between the two sides of 3 ml and over are pathological.

There is no difference in the threshold values for males and females. The explanation why previous workers have found such a sex difference is presumably that they have used M.I O., not M.P O and that they have used test substances better known by women than by man

Brief Anatomical Review of the Sense of Smell:

The olfactory nerves penetrate the lamina cribrosa, forming in the olfactory bulb which lies on the lamina cribrosa, the first synapsis with extensions from mitral cells and tuft cells. These synapses are called glomeruli. From the mitral cells and tuft cells the nerve fibres proceed through the olfactory tract, which is situated in the olfactory sulcus on the under aspect of the frontal lobe to the olfactory tubercle and trigonum where they divide into the lateral and medial olfactory striae. The olfactory trigonum and tubercle are situated just lateral to the optic chiasm. Some of the medial fibres cross through the anterior commissure while by far the greater part of the fibres from the olfactory bulb proceed to the homolateral side. From the named structures other nerve fibres proceed, but their course is only partially elucidated, and they must be assumed to be largely of significance to various olfactory reflexes, having nothing to do with the perception of smell. It is of importance in testing the sense of smell that large parts of the rhinencephalon have no relation to the sense of smell, but that the olfactory primary centres comprise only the uncus and the anterior part of the gyrus hippocampi. Therefore, only those nerve fibres which end there take part in the sensation of smell. The secondary centres comprise the adjacent parts of the temporal lobe in which the analysis of the impulses and their integration with other impulses must be assumed to take place

In this context, we are interested only in olfactory disturbances due to intracranial diseases.

Elsberg was the first to demonstrate that by combining tests of threshold values and of olfactory fatigue it is often possible to arrive at a more exact intracranial local diagnosis.

The principle of this testing is that a lesion of the external olfactory pathways, i.e. the olfactory nerves, olfactory bulb, olfactory tract, and of the medial and lateral olfactory triae leads to elevated threshold values on the homolateral side while fatigue is normal. On the other hand, a lesion of the internal olfactory pathways will result in normal threshold values, but in a prolongation of the fatigue on the homolateral side In diseases involving both the external and the internal olfactory pathways, there will be an elevated threshold value as well as a prolonged fatigue These results were confirmed in our studies.

For testing the olfactory fatigue the apparatus is fitted in a different way Instead of being connected to the glass syringe the corresponding rubber tube is connected to a container holding compressed air and by inserting a flowmeter it is possible to measure accurately the quantity of air passing through the apparatus

The procedure of determining olfactory fatigue is then First, the threshold values on both sides are determined in the usual way Thereafter the patient places the nose piece into one nostril as usual directed towards the olfactory region, and a current of air of 2,000 ml per minute is passed through the apparatus and the corresponding nasal cavity for exactly half a minute The patient closes the other nostril with a finger and breathes quietly through the mouth After the [illegible] has been removed, the apparatus is fitted again for determination of the [illegible]

value, and every half minute the olfactory region concerned is stimulated by the already determined threshold value, until the patient states that he can smell it for 3 times running The time which elapses until the patient first states that he can smell threshold values is, then the fatigue measured in minutes.

Unlike the threshold values, the olfactory fatigue does not increase with age

Differences between the two sides of more than 1 1/2 minute are pathological.

However the testing for olfactory fatigue is slow and requires particularly good cooperation on the part of the patient, and this is only possible in about 60 % of patients with intra-cranial tumours.

The most important part of testing the sense of smell is determining the threshold values in the event of the slightest suspicion of basal processes in the anterior part of the base of the skull, in which a unilateral hyposmia is often the first and only sign for a long time. There may for instance be as question of basal tumours of the frontal lobe, of meningiomas from the lamina cribrosa and the ala parva and parasellar tumours. Unilateral hyposmia which is not explicable by local nasal diseases, should always give rise to a suspicion of intracranial disease.

The distinction between real and non-real hyposmia is of great medicolegal importance, especially after cranial injuries.

Two different principles are available:

1) The influence of the sense of smell upon various vegetative functions, int.al. the olfactopupillary reflex (Luchsinger 1940), a psychogalvanic test of smell (Semeria 1956), and alterations in the blood flow following stimulation of the olfactory sense (Kottmeyer 1957)

2) Alternation between pure olfactory stimulants and mixed olfactory trigeminal stimulants.

In general it is sufficient to alternate between pure olfactory stimulants and mixed olfactory trigeminal stimulants as done by us in the previously mentioned testing with the 8 odorous substances. The non-real patient will nearly always state that he can smell nothing while the patient with real anosmia states, it is true, that he cannot smell anything, but the trigeminal stimulants give him some sensation in the nasal cavity owing to their stimulation of the peripheral trigeminal end organs.

Psycho-galvanic testing of the sense of smell, like the psycho-galvanic hearing test, has also proved useful in our hands, especially for determing thresholds.

Quantitative testing of sensibility in the trigeminal area is done with a Boberg-Ans corneal sensibilometer This apparatus utilizes a nylon thread which may be varied in length and thereby in strength of stimulation. The apparatus was originally designed to measure corneal sensibility but it can also be used for measuring sensibility on the skin and mucous membranes in other sites.

Corneal sensibility is often reduced in the presence of lesions in the cerebello-pontile angle, and in their early stages this is demonstrable only by a quantitative test

Less quantitative disturbances of sensibility may be found in morbid processes in the central course of the trigeminal nerve, e.g. tumours in the middle cranial fossa.

A quantitative test of the nasolacrimal reflex is also included in the testing of the trigeminal nerve and, moreover in the testing of the facial nerve.

The nasolacrimal reflex (NLR) consists of lacrimation following chemical or mechanical stimulation of the nasal mucosa.

Fig. 2. Diagram of th course of nasolacrimal reflex arch (heavy lines).

The first and second branches of the trigeminal nerve form the afferent paths. The efferent paths proceed from the superior salivatory nucleus through the facial nerve (nervus intermedius) through the geniculate ganglion, the greater superficial petrosal nerve, and the nerve of the pterygoid canal to the sphenopalatine ganglion from which it proceeds through the sphenopalatine nerves to the maxillary nerve and *via* the zygomatic nerve to the lacrimal nerve and lacrimal glands.

It has been discussed whether the nasolacrimal reflex are really did run this course, but according to our quantitative tests of the nasolacrimal reflex before and after cutting the facial nerve between the geniculate ganglion and nucleus and cutting of the trigeminal nerve central to the semilunar ganglion the reflex are does run the course decribed above.

For testing the nasolacrimal reflex (Fig 3), the Elsberg olfactometer is fitted for fatigue testing as previously described. The bottle is filled with 30 ml pure ben zine which is a potent trigeminal stimulant. Thereafter a current of air of 500 ml per minute is passed through the bottle, and through the nasal cavity where the nose piece has been placed, for exactly half a minute As the stimulation is started,



Fig. 3. Apparatus for measurement of the nasolacrimal reflex.

a piece of filter paper is placed by the method of Schirmer into the inferior conjunctival fornix, folded twice at right angles. The filter paper is removed half a minute after the stimulation has been discontinued and when it has dried, the quantity of tears may be measured in mm

Statistical calculation of our normal material is of significance in this connection as differences of more than 20 / between right and left are pathological.

Testing of the nasolacrimal reflex is of importance in lesions affecting the intra cranial course of the trigeminal nerve e.g in meningiomas of the middle cranial fossa In 21 cases of meningioma in this site we have found a greatly diminished nasolacrimal reflex to be the only otoneurological sign.

Moorever the nasolacrimal reflex is diminished in the presence of diffuse lesions of the brain stem e.g pontile gliomas. In such cases it may possibly be reduced on both sides.

Lastly the testing of the nasolacrimal reflex is of significance in diseases which involve the facial nerve between the nucleus and facial ganglion, i.e. primarily processes in the cerebellopontile angle, including acoustic neurinomas.

This leads us to testing of the facial nerve.

In the internal acoustic meatus the intermediate nerve courses, as suggested by its name between the motor part of the facial nerve and the eighth cranial nerve. An acoustic neurinoma nearly always gives rise to changes in the inter mediate nerve before the motor function of the facial nerve is affected, which is a late sign in these tumours.

Among 54 cases of acoustic neurinomas confirmed by operation 22 had reduced acoustic vestibular function and reduced function of the intermediate nerve as the only neurological signs. All 22 patients had definitely reduced nasolacrimal reflex, and 15 of them also a decreased sense of taste on the anterior two-thirds of

the tongue. The motor function of the facial nerve was normal in all 22. Therefore it is important to test, apart from the acoustic vestibular function, also the naso-lacrimal reflex and taste if there is a suspicion of acoustic neurinoma, since it is of the greatest therapeutic importance that these tumours be diagnosed as early as possible.

For testing taste we use partly Börnstein's semiquantitative test and partly an electrogustatory test with galvanic current. In the Börnstein method we have 3 different concentrations of sweet sour salt and bitter shown in Fig 4 the



Fig. 4. Testing the sense of taste on the anterior two-thirds of the tongue using various solutions of sweet, sour salt and bitter

patient puts out his tongue which is grasped with a piece of gauze held beneath the tongue. Thereafter a drop of the solution is dropped on the lateral edge of the tongue, so that the fluid does not flow to the contralateral side. The piece of gauze also prevents it from flowing under the tongue down to the floor of the mouth. It is very important to carry out this procedure with accuracy as many unnecessary discussions on the sense of taste have been caused by a poor technique with overflow of the gustatory substance from one side of the tongue to the other While his tongue is out, the patient is asked to point at a slip of paper with the words sweet, sour salt, bitter and water With curved pipettes it is possible to test the taste on the posterior third of the tongue, whence the gustatory fibres course through the glossopharyngeal nerve. This is one of the most important methods of testing the function of this nerve.

For a more accurate testing of differences between the two sides of the tongue, we use an electrogustometer which, in its present shape, was designed by Krarup

The threshold values are given in microamperes. Krarup has introduced a special electrogustatory unit, so that the percental increase between the various stimuli is the same. However, the threshold values may still be stated in microamperes, and Krarup's normal material has shown that differences between the two sides exceeding 40 % are significantly pathological. The electrogustometer is best used for the anterior two-thirds of the tongue, as application to the posterior third is difficult and this part should be tested by the Börnstein method.

Stapedial function is tested by Scott Nielsen and Terkildsen's electroacoustic bridge.

By combining the testing of the nasolacrimal reflex, taste, and stapedial function, we can divide the total peripheral facial palsies into (Fig. 5):

A nuclear
B suprageniculate
C suprastapedial
D infrastapedial
E infrachordal

In this connection the nuclear and suprageniculate palsies are of most interest. Tumours in the cerebellopontile angle have already been mentioned. Nuclear palsy may be observed in the presence of infectious, neoplastic, and degenerative processes in the pons. In poliomyelitis we have seen total peripheral facial palsy in

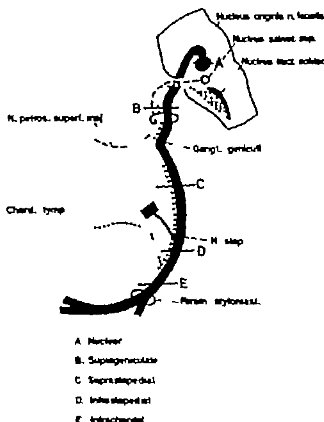


Fig. 5. Diagram of nerve pathways of importance in the topographic diagnosis of peripheral facial nerve palsy

which stapedial function was invariably abolished. A few of the patients also had abolished nasolacrimal reflex, but all had a normal sense of taste.

In peripheral posttraumatic facial palsy there is often no help to be had from testing stapedial and gustatory function because of the frequently concomitant traumatic changes in the middle ear. In such cases, testing of the nasolacrimal reflex may be able to decide whether the injury is situated above or below the geniculate ganglion and thereby indicate which operative procedure is to be selected in a possible surgical treatment of facial palsy.

Every otoneurological examination should be finished by a conclusion which should include the history and the investigations done (in our Department usually ophthalmological examination, X rays of the skull without contrast medium, neurological examination and EEG) in relation to the otoneurolgical findings and also to the very important testing of the acoustic vestibular function.

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CLINICAL VESTIBULAR EXAMINATIONS AND THEIR RESULTS

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Electronystagmography gives objectivation and documentation to the clinical vestibular otoneurological tests. With fixation eliminated the duration of calorically and rotatory induced nystagmus is 30 per cent longer and the speed in the slow phase of this nystagmus up to ten times that recorded under Frenzel's glasses.

In a large series of patients only one out of ten cases of spontaneous or positional nystagmus recorded behind closed eyelids could be observed directly. At an acute onset of vestibular symptoms the visual influences are negligible, if the onset is insidious or the interval between onset and examination is longer this visual inhibition is more pronounced.

It is a reasonable safety requirement that the same examiner should be equally well orientated in both the audiological and vestibular function tests. The diagnosis of a central vestibular lesion cannot be established until the possibility of the findings being of peripheral origin has been excluded. This latter conclusion usually has to be based on the audiological findings.

Calorization yields more from the diagnostic aspect than a rotatory test. After comparing calorigrams and cupulograms in 5,000 patients, this rotatory test was dropped.

The experiences of electronystagmography from the diagnostic point of view in 30,000 patients are summarized

Clinical neurological examination methods are motivated only if their aim is to reach a *topical or systemic diagnosis*. For this purpose thorough knowledge of the anatomy and physiology is essential. A simple illustration, in our field is the level localization in facial paralysis. Regarding the vestibular nerve and its central connections, however our knowledge is incomplete. The neuro-anatomical investigations carried out by Brodal and his collaborators have shown that after section of the vestibular nerve the terminal degeneration reaches only parts of the so-called central vestibular nuclei. The outer part of the superior nucleus, the entire dorsal part of the lateral nucleus, the medial part of the triangular nucleus and the lateral parts of the descending nucleus remain unaffected. Some fibres on the other hand, pass directly as far as to certain well-defined areas of the cerebellum, viz. the ipsilateral flocculus, paraflocculus, uvula nodulus and lingula. Neither this technique nor any other has provided information about how the *five labyrinthine end organs*, i.e. the three *cupular organs* and two *maculae* are projected in the areas mentioned, or as to the possible existence of a somatotopical functional organization.

In the clinic this means that when stimulating any one of these end organs, e.g the ampullar end organ of the lateral semicircular canal by *rotation or calorization*, or the macula in a positional nystagmus test, we do not know the primary reflex arc. Investigations by Szentagothai, Bender Fluur and others have shown a func

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tional correlation between, for example each ampulla and the different ocular muscles. However the events between these two terminations of the nystagmic reflex are very obscure. The possibilities of arriving at a topical diagnosis will probably increase greatly when the function of the different components of the central reflex are becomes known.

Nevertheless vestibular examinations have increased in clinical value This is due to improvement in clinical vestibular tests, with standardization of the stimuli used, new possibilities of analysis and documentation of the results, a better understanding of the peripheral vestibular function and refinement of the cochlear tests. The diagnosis of a central vestibular lesion should be based primarily in my opinion, on the exclusion of a peripheral pathogenesis. Only if the audiological findings are normal, can this exclusion be made with any degree of certainty Just as the vestibular examination should not be allowed to become merely a test for nystagmus alone so will the diagnostic results also be poor if the audiologist neglects the vestibular tests in retrocochlear nerve deafness.

Audiologists without basic medical and otological training are to be found in some countries, and when their work involves a neurological diagnosis, difficulties are sure to arise As an example I will mention House s presentation of his series of acoustic tumours. No audiological test gave significant results in more than 72%. Vestibular findings were present in 96%, but no further analyses were made With due respect to House and his excellent work, I feel that far better diagnostic results would be obtained if one and the same examiner with the same interest performed both the cochlear and vestibular tests. In the last two years we have seen four patients in Uppsala with tumours in the internal acoustic meatus or pons angle, where one or several years previously a retrocochlear nerve deafness had been diagnosed but no vestibular tests performed, and consequently no tumour was discovered. By the time we examined the patients they were completely deaf and the diagnosis was based on vestibular tests and loss of function from other cranial nerves within the sphere of oto-neurology The tumours included acoustic neurinomas and a basal meningioma. In the patient with meningioma the symptoms had begun ten years earlier and the audiologic diagnosis of retrocochlear deafness was made three years before the operation. Radical surgery was not possible at this time, though it might have been some years before. It is easy of course, to be wise after the event, but the conclusion must be drawn that a sub-specialization (as audiology is) has its dangers, and that as long as a neurologic diagnosis is the aim, vestibular and audiologic tests must be kept together

A neuro-otologic examination should include the following components, the selection of which is based on 20 years experience from the Uppsala Ear Nose and Throat Clinic.

1) Checking of the case history especially in patients referred from non-otologists.
2) Otorhinolaryngologic routine examination, including tests of motor and sensory function.
3) Fistula tests, not to be forgotten in »otologic« patients.
4) Pure tone audiometry If the results are not normal it should be followed by Fowler s balance test and/or Békésy Jerger audiometry and speech audiometry

5) Positional test with nystagmography behind closed eyelids and also examination with Frenzel's glasses. Test with eccentric fixation with positive findings, test with and without neck torsion also
6) Calorization *ad modum* Hallpike, but with 30 seconds irrigation and nystagmography. When necessary tests with iced water and arousal maneuvres.

If the standard procedure in this scheme gives normal results, the risk of making serious mistakes will be reduced within reasonable limits. On the other hand positive findings of any type may require variations in the examination such as those mentioned in the above list of tests.

No rotation tests are included. This has been decided as a result of an investigation in which cupulometry was performed simultaneously with the Hallpike method of calorization on 5 000 patients. It was concluded that cupulometry especially the sensation cupulogram, involved several errors, and that more was gained and nothing lost by calorization. Cupulometry also demands a technical apparatus that is only possible in a few research institutes.

The neuro-otologic examination in itself is very time-consuming, even though some parts can be performed by technical assistants. It is also rather exhausting for the patient and there should be very strong reasons for the addition of extra details. In clinical work much more would probably be gained if the basic examinations mentioned above were carried out with the utmost care; instead the trend sometimes seems to be to add more and more complicated tests, demanding additional equipment.

The observation of nystagmus and the evaluation of induced nystagmus play such a dominating part in the vestibular examination that the following presentation will be limited to these factors and to nystagmography. Is it really necessary to include nystagmography in the routine examination and what will be gained? My answer is an unrestricted yes, for the following reasons.

Nystagmography gives an objective documentation, and that is reason enough, but there are even stronger arguments. Neuro-otology involves the study of

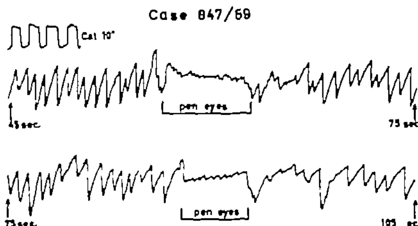


Fig. 1. Visual influence on calorically induced left beating nystagmus recorded behind closed eyelids with the exception of the periods marked open eyes. Note the decrease in the intensity of nystagmus during these periods. Time marking from starting the syringing for 30 sec.

nystagmus as a spontaneous symptom or a labyrinthine reflex response. It is thus essential to study this reflex uninfluenced by other stimuli, above all ocular factors. Let us see what happens to a calorically induced nystagmus recorded under different visual conditions. Figure 1 shows such a left-beating nystagmus recorded behind closed eyelids. For a first period of 5—6 seconds the subject is then looking up and then for a second period the same length of time looking up under Frenzel's glasses. During the period with visual influences the intensity of the calorically induced nystagmus is reduced to 1/10 or less of the original. In rare cases the opposite may be recorded, and such an observation also has a diagnostic value. The patient's state of wakefulness may be lowered and «arousal maneuvres» such as giving mathematic problems to solve not seldom have to be used to obtain true answers and recordings. Slow pendular eye movements resulting in a sinus wave-like recording is probably an expression of the same phenomenon. The first record in Fig. 2 shows a normal recording behind closed eyelids in a normal test subject. Ten minutes later with the subject in deep hypnosis, a «sinus curve» is recorded. A rotatory stimulus can act as an arousal maneuvre in these normal subjects. In a patient with markedly slow cerebration due to cerebral metastases from a breast cancer (Fig. 3) the same type of sinus wave-like record was obtained. Here a caloric stimulation produced an arousal effect. The last record in this figure was included because it shows a marked dysrhythmia in the calorically induced nystagmus, which is fairly often seen in patients where the state of wakefulness is affected, e.g. by tumours, drugs or other factors. All the information obtained from these records can only be obtained by using nystagmography.

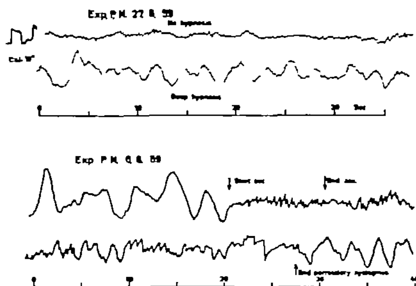


Figure 2. The two records on the top show «sinus curve» provoked by deep hypnosis. The two other records the same slow pendular eye movements in the same test subject. A rotatory stimulus here acted as an arousal maneuvre and at the end of the last record the «sinus curve» appears again.

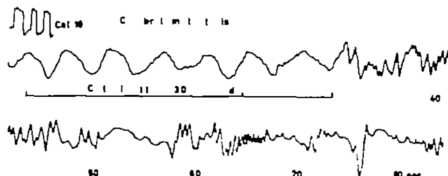


Figure 3. Slow pendular eye movements in patient with marked slow cerebration due to cerebral metastases. The caloric stimulus here gave an arousal effect but marked dysrythmia in the calorically induced left-beating nystagmus is easy to observe in the last part of the record.

Nystagmography provides the possibility of studying not only the beat direction of the nystagmus but also of evaluating the records quantitatively. A simple calibration method gives information about the intensity of the nystagmus as eye speed in the slow phase, but other parameters such as beats per second, total amplitude and duration can be calculated. Thus an asymmetric response to calorization can be established by several parameters, and this is of especial value when a nystagmus is present in the test position before the irrigation is begun. Only by nystagmography is this possible.

The influence of fixation on vestibular nystagmus can also be determined quantitatively. In a normal material Aschan, Bergstedt and Stahle (1956) using the Hallpike technique but with irrigation for only 30 seconds obtained, by nystagmography without fixation, mean duration values of 175 seconds. Despite an irrigation period of 40 seconds — i.e. stronger stimulation — Cawthorne, Fitzgerald and Hallpike, with fixation and direct observation, noted mean values of 110—120 seconds. Thus about 1 minute, or 30 per cent of the nystagmic response is lost. The same also holds for the duration of nystagmus induced by rotation. The fact that the intensity of vestibular nystagmus, measured as the eye speed in the slow phase, is also decreased by fixation, has already been demonstrated in Fig. 1. Aschan, Bergstedt and Stahle (1956) showed that fixation reduced the intensity to about 1/10 of its pre-fixation value. This observation has been verified during the last few years in a large series of investigations using nystagmography.

Much information has been gained from patients with spontaneous or positional nystagmus whom it has been possible to follow up repeatedly over a long period of time, recording the nystagmus under different visual conditions. Figure 4 shows, as a very typical example, a left-beating spontaneous nystagmus after a right-sided labyrinthine destruction. 16 months after the onset of the spontaneous nystagmus it could still be recorded with the same intensity behind closed eyelids. Behind Frenzel's glasses an increasing inhibition of this nystagmus was noted, and 4 months after the operation this method indicated that the spontaneous

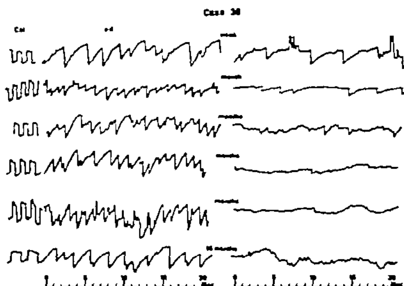


Figure 4 A left-beating spontaneous nystagmus following right sided labyrinthine destructi recorded without and with fixation at intervals after the operation. The so-called central com pensation when using Frenzel s glasses is nothing but visual inhibition. The calibrations to t left refer to 10 degree ey movements and mak it possible t compare the records quantitativel

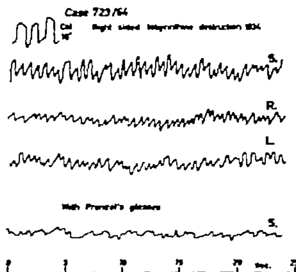


Figure 5. A pontaneous left-beating nystagmus following fracture 30 years before these recor were made 1961. S R and L supine right lateral and left lateral position of the head. Th fir three records were mad behind closed eyelids. Compare t figure 4.

nystagmus had disappeared. The so-called central compensation of the labyrinthi destruction nystagmus is nothing but inhibition by fixation. The significance c *this in clinical diagnosis can be seen in Fig 5 which refers to a patient first see* in 1964 and in whom a left beating nystagmus was recorded without fixatio

In 1934 i.e. 30 years before our examination, he had fallen 16 metres and a fractured base of skull was diagnosed. His recovery was slow and incomplete. During these 30 years he had had 12 special otologic examinations. In all of these a right-sided moderate nerve deafness was the only positive finding. No comments were made as regards nystagmus, and apparently he had never had a caloric test. No Weber test or audiogram had been done. Now he shows lateralization to *the left ear in the Weber test. Syringing of the right ear does not influence his* nystagmus, whereas syringing of the left ear changes the nystagmus according to the rules. X-ray of the skull still shows the right-sided fracture line pointing to the temporal bone. Without question his right labyrinthine function was destroyed in 1934 and this has remained undiagnosed for 30 years. The nystagmus recorded in 1964 had been present for 30 years! Every year we encounter some cases like this one, but this is the longest interval we have found between trauma and diagnosis.

In Uppsala we record spontaneous and positional nystagmus both behind closed eyelids and under Frenzel's glasses. As an approximation, out of 100 positive observations behind closed eyelids only 10 can be verified with Frenzel's glasses. Over-diagnosis may be suspected by critical persons. Jongkees and co-workers (1962) suggested that the explanation was to be found in the intensity of the spontaneous or positional nystagmus.

Repeated tests performed over a long period of time on patients with labyrinthine

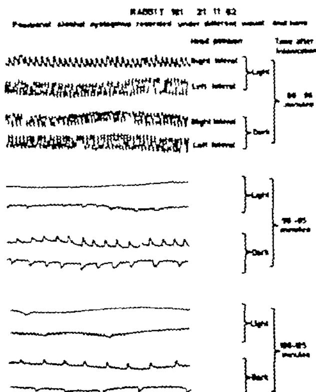


Figure 6. Positional alcohol nystagmus in a normal rabbit recorded with fixation in light and without fixation in complete darkness. Fixation gives inhibition of nystagmus just as in man.

destruction and on those with Meniere's disease during and after attacks (Aschan & Stahle 1957), and also the nystagmographic follow-up of patients treated with ultrasonic labyrinthine destruction (Sjöberg, Stahle et al. 1963, 1964) all show that an initially observed nystagmus can be recorded by nystagmography without fixation for a considerable length of time after it has ceased to be seen by direct observation.

This is the best argument against the suspicion of over-diagnosis as a risk in nystagmography

It is perhaps worthy of note that in experimental animal studies the same inhibition of vestibular nystagmus is observed in both acute and chronic conditions. Figure 6 shows a positional alcoholic nystagmus in a rabbit On direct observation it is found that this nystagmus disappears at a blood alcohol concentration of 0.24 per cent using nystagmography in complete darkness the corresponding blood alcohol value is only 0.12 per cent. In a chronic experimental condition as shown in Figure 7 the nystagmus from a central vestibular lesion can only be observed in complete darkness. The inhibition of vestibular nystagmus thus influences the experimental results (Aschan Grant & Ekvall 1964) a considerable source of error which may explain several of the contradictory findings in experimental research

In the clinic there are two predominant factors to be considered concerning the question of whether a nystagmus can only be recorded behind closed eyelids or also by direct observation. The first is whether or not the onset of the symptoms is acute, and the second is the length of time that has elapsed between the onset and examination. Figure 8 illustrates a case with an acute onset and with a moderate length of time between onset and examination. This elderly lady with hypertonia became acutely ill during an agitated discussion with a tax inspector She was unable to stand, she vomited, and complained of headache and vertigo One hour later a left-beating spontaneous nystagmus was observed directly by her physician. The recordings in Fig 8 were made one week after her sudden illness,

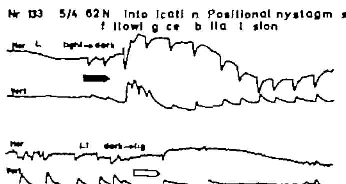


Figure 7 A nystagmus in rabbit due t cerebellar lesion. This nyst gmus seemed to have disappeared i few days but in darkness without fixation the same nystagmu could be recorded until the animal was killed.

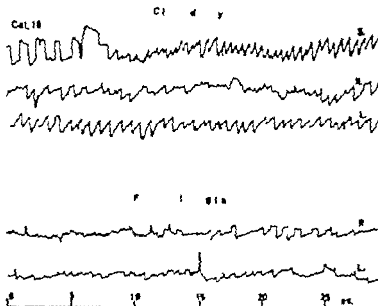


Figure 8. A positional direction-fixed left-beating nystagmus due to a vascular lesion in the central nervous system one week before records were made. Note the differences between the two R and L records recorded without fixation and those recorded under Frenzel glasses with visual influences as a source of error

by which time she had recovered subjectively Under Frenzel's glasses only a few beats to the left were observed and recorded in the left lateral position. Without fixation however a left-beating and rather intense positional nystagmus was recorded and this was present for a year even at her last examination, when nothing was observed under Frenzel's glasses.

Fairly often there is no acute onset and in these cases the risk of overlooking a nystagmus increases greatly if nystagmography with fixation is used. One example out of several is shown in Fig 9 This female patient had one single grand mal attack, headache and severely pathologic EEG findings at several examinations, but nothing abnormal neurologically Nystagmography without fixation revealed a *right-beating positional* nystagmus which was not *observed under* Frenzel's glasses, and a directional preponderance to the right, well marked in the intensity of the calorically induced nystagmus. Neuroradiology and operation showed a right-sided temporal lobe tumour

From the Uppsala series of about 30000 *neuro-otological examinations carried* out with nystagmography we have learned that the combination of a positional or spontaneous nystagmus with a directional preponderance in the caloric test *is of much greater diagnostic value than a directional preponderance alone* when the same technique is used Figure 9 is a typical example of a patient in whom direct observation could have revealed only directional preponderance.

A *spontaneous or positional nystagmus with symmetric caloric reactions* has also been shown to have a much higher diagnostic value than a directional preponderance as a single positive finding Here, however other factors must be

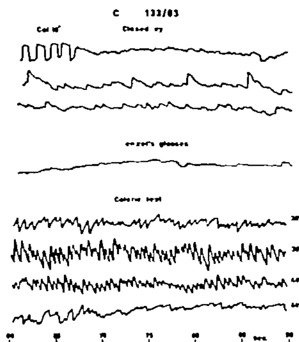


Figure 9. Right-sided temporal lobe tumor The positional direction fixed right-beating nystagmus could not be seen or recorded when using Frenzel' glasses. The four part f the calorically induced nystagmus refer t the same period 60—90 sec after th beginning of th four different irrigations included in the Hallpike test. The directional preponderance to the right is easy to see in the intensity As there was no nystagmus in the position for the caloric test the differences in intensity are significant.

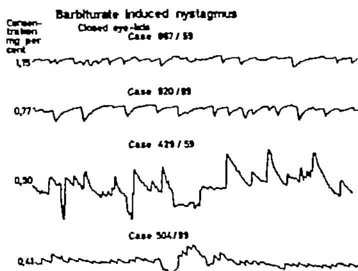


Figure 10. Four patients in whom the nystagmus records could be attributed to barbiturates. The actual blood concentration of barbiturate in each patient is gi en t the left. When free from barbiturat the patients had no nystagmus.

considered when using nystagmography We collected a consecutive series of such patients during a period of 18 months until a total number of 100 was obtained As routine they all had a blood sample taken for a barbiturate test. 68 per cent of them had barbiturates in the blood 42 per cent with concentrations of 1 mg or more. Some typical records are shown in *Fig* 10 Unfortunately barbiturates do not give such a typical pattern of nystagmus as alcohol. When the barbiturate medication was eliminated the nystagmus disappeared within a period of 24 hours—2 weeks depending on the type and amount of barbiturate used. Of the remaining 32 patients we have only been able to follow up 20 During the observation period of eight years 8 of these patients, all of whom were 14—26 years old at the first examination, later developed a clear clinical picture of multiple sclerosis. For years the nystagmus was their only symptom and it was not until later that the suspicion of »over-diagnosis» could be dismissed. In two patients tumours have been discovered. In the remaining 10 patients either the nystagmus has disappeared or its pathogenesis is still undecided.

Even if the consumption of barbiturates may decrease the therapeutic arsenal shows an increasing number of drugs acting on the central nervous system several of them having effects or side effects on the vestibular apparatus. This gives the neuro-otologist so many difficult problems in his clinical diagnostic work that it is worthy of a special warning With questionable or peculiar findings which have been difficult to explain, the precaution of a repeated examination some days later after depriving the patient of any medication, has very often cleared up the situation.

Patients with a directional preponderance as the single positive finding and where a central vestibular lesion or functional disorder has thus been suspected have not been too numerous. On the other hand this group represents those patients where the follow up examination, using the nystagmographic technique, has given no certain diagnosis. Changes of the canal paresis type with or without positional nystagmus has terminated with a definite diagnosis in nearly all cases or the changes could be attributed to anatomic asymmetries in the temporal bone.

As a closing remark, labyrinthine vestibular disorders, and to some extent lesions of the eighth nerve outside the brain stem, are not too difficult to diagnose The diagnosis of central vestibular disorders will be made, as a rule, by excluding the possibility of a peripheral pathogenesis. This demands a most careful audiologic examination combined with vestibular tests. In the vestibular examination nystagmography without fixation gives so many advantages that there is all justification for including it as a routine measure. I have made a special attempt to illustrate this here, as I consider that it is in nystagmography that we have gained most in the last decade. However it is dangerous to make a specified topical diagnosis of central lesions from vestibular examinations alone Such a diagnosis is usually justified only in the presence of neuro-otologic findings from other cranial nerves. On the other hand vestibular findings alone that are suspected to be of central origin usually have to be followed by continuous observation, neuro-radiology and so on, but this is the responsibility of the internist, neurologist or brain surgeon, and not the otologist.

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DISCUSSION

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Dr Kierboe Chief of the Aviation E.N.T. Department of the Rigshospital, Tagensvej Copenhagen has, asked me to state that his experiences are in agreement with those of Aschan. During his examination of student pilots for the Air Force (a total of 4,000 in the course of about 12 years), not less than 40 showed either spontaneous or positional nystagmus. The condition was monosymptomatic and could be found on repeated examinations, without the use of E.N.G. but by observation with Frenzel' spectacles alone. None of these persons was under the influence of drugs or alcohol, and none had been exposed to recent cranial traumas.

All these candidates were rejected for service in the Air Force, which was fortunate, in that subsequently ten of those who reported for follow-up were found to have definite signs of disseminated sclerosis.

The Danish Clinic of Aviation Otology and the Military E.N.T. Department of the University Hospital (Rigshospital Tagensvej) have always regarded the presence of spontaneous or positional nystagmus in otherwise normal persons as a pathologic phenomenon. The concordance between the various study materials submitted here strengthens that attitude considerably.

Stahle was not able to demonstrate (even by E.N.G.) spontaneous or positional nystagmus in 50 young normal persons. In contrast, the Amsterdam group including Jongkees and Philipszoon, found up to 30 per cent of normal persons with that phenomenon. The difference is so great that there must be divergence in selection of the material or in evaluation of the E.N.G. findings. It would be desirable if this problem could be elucidated further from the point of view of selection of normal material and assessment of results, and we consider this to be of great importance.

As regards vestibular tests, we think it would be less confusing if Hallpike' name could be used only in connection with his special method (direct observation while the patient's eyes are focussed on a spot on the ceiling and with flooding lasting 40 seconds). Even if it is explained that different times and methods for observation and registration are used, many listeners might perhaps attach more importance to the name Hallpike. We would suggest, therefore, that Hallpike' name should be used only when referring to tests which fulfil his criteria, and that other methods should be called »quantitative caloric tests».

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Electro-nystagmographic (ENG) examinations are very essential, but I am afraid that many doctors think that they can not do a good vestibular examination without ENG. In most cases it is possible to make a sufficient vestibular testing with examinations of spontaneous, positional and optokinetical nystagmus and doing a differential-caloric test, and it is possible e.g. to diagnose all acoustic neurinomas without ENG. Only in this way we get the tumors early enough. The differential caloric test a.m. Hallpike is done with the eyes opened and fixing the gaze on some convenient point in the ceiling in the center of the visual field. If the examination is done with the eyes closed or by using Frenzel' glasses it is not a Hallpike test and the result of the examination can be very misleading and e.g. in temporal tumors you can find a preponderance to the opposite side of the tumor as shown by Hallpike et al. using DC-ENG (in a paper published in Brain some years ago).

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RESULTS OF PARTIAL OR TOTAL NERVUS OCTAVUS SECTION IN PATIENTS WITH MÉNIÈRE'S DISEASE

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A follow-up examination of 36 patients with Ménière's disease treated from 1944 through 1965 by intracranial partial or total section of nervus octavus has shown:

1) Vertigo: All the patients have obtained *complete relief from attacks of vertigo.*
2) Tinnitus: Tinnitus has *disappeared or decreased in about 2/3 of the patients.*
3) Hearing: *Useful hearing can be preserved by partial (vestibular) section of nervus octavus.*

Of the many *forms of surgical therapy* used in the *treatment of Ménière's disease* the intracranial partial (vestibularis) or total section of nervus octavus *shall be* dealt with here. This operation was first performed by Frazier more than 50 years ago. Later Dandy, McKenzie and, in Scandinavia, Olivecrona have used this operative technique on a considerable number of patients. A large proportion of Dandy's patients and the great majority of those of McKenzie and Olivecrona underwent partial (vestibularis) section of the eight nerve.

From follow-up examinations of a considerable number of Dandy's and McKenzie's patients (Green & Douglass, 1951, Barber & Ireland, 1952) it appears that 1) the great majority of these patients have been relieved of attacks of gyratory vertigo, that 2) tinnitus has been completely or partially relieved in a considerable number, and that 3) a useful hearing — at least for pure tones — may be preserved for a number of years if partial section of nervous octavus is performed.

However, in recent years the interest in this operative form of treatment has been completely overshadowed by the interest in other treatment methods, e.g. ultrasonic therapy.

Nevertheless, Fluur and Tovi (1965) have recently reported on 7 patients who underwent vestibular section under microscope. The use of a microscope ensures a precise section of the vestibular part of nervus octavus, since the demarcation line between the two parts can be more clearly seen. We have therefore made a closer study of our material operated with the same technique, with the sole difference that magnifying glasses instead of operation microscope were used.

During the period 1944—1965, 42 patients underwent partial or total section of nervus octavus owing to unilateral Ménière's disease in the neuro-surgical department of the *Aarhus Kommunehospital* giving an annual average *of 2—3* operations.

In the present paper an account shall be given of the results of a follow-up examination of 36 of these patients, 19 of whom underwent partial (vestibularis) and 17 total section of nervus octavus. The material consisted of 15 women and 21 men from 24—71 years of age, the average age thus being 46 All patients presented the classical triad of symptoms. loss of hearing of the perceptive type, tinnitus, and incapacitating attacks of gyratory vertigo which had proved refractory to conservative treatment.

Regarding the operative technique used it should be briefly mentioned that for purposes of the operation a small craniotomy is performed above the posterior fossa. With magnifying glasses it was usually possible to see a distinct line of demarcation between the vestibularis and the cochlear part of the nerve. Of operative findings it should be mentioned that in one case the eighth nerve was found to lie in the floor of an arachnoid cyst In contradistinction to the rest, this patient had no recruitment, for which reason it may be assumed that it was not a case of real Ménière s disease. The follow-up examinations were performed from 9 months to 22 years after the operation and the results as to vertigo, tinnitus, and hearing are as follows.

A Vertigo

Total Section

	Attacks of gyratory dizziness	Uncharacteristic attacks or instability on change in position and/or in dark
17 pt.	0	11
Partial Section		
19 pt.	0	15

It will be seen that total as well as partial section relieves the patients of attacks of gyratory vertigo, which in many of the patients were severely incapacitating As shown, 26 patients still suffer from slight instability on changes in position and/or in the dark, but only in one patient was it so severe as to render him unable to work. In spite of this the patient was grateful to have been relieved of his attacks of gyratory dizziness. It should, however be mentioned that in this latter case the period of observation was only 9 months. In addition, 3 patients have had slight attacks of instability which were not described as gyratory and which have not affected their ability to work. In one patient attacks of gyratory vertigo reappeared after a couple of years, but were elicited from the other ear

In one patient, in spite of assumed total section of nervus octavus, there was caloric response in the operated ear but weaker than in the other ear In spite of this finding the patient has been relieved of attacks of gyratory vertigo In 20 patients there was fine and in some cases intermittent spontaneous nystagmus away from the operated ear

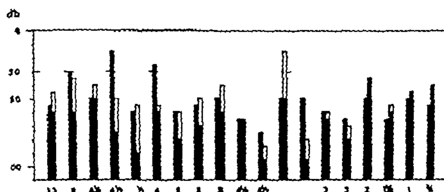
B Tinnitus

	Ceased	Decreased	Unchanged	Worse
Total Section				
17 ptt.	1		3	0
Partial Section				
19 ptt.	7	4	6	2

It will be seen that total section has undoubtedly a better effect on tinnitus than partial section. Similar findings have been demonstrated by Green and Douglass in their follow up examination of Dandy's patients.

C Hearing

From the diagram (Fig 1) it will be seen that in 13 of the 19 patsents undergoing vestibular section, the difference between the pre- and the post-operative hearing



19 patients treated by section of the vestibular nerve. Each patient is represented by two columns. The first indicates the preoperative hearing (in average for the speech frequences). The second the postoperative hearing. The white part of the column stands for the hearing loss from the first examination 6—8 months after the operation until the follow-up examination. The numbers beneath the columns indicat the follow up time in years.

is 10 decibel or less at the examination 6 months postoperatively At this time the hearing had improved more than 10 decibel in 3 patients and had decreased by more than 10 decibel in 3 patients. However at follow up examination 4—13 years after the operation, 9 patients showed a considerable decrease in hearing (10 decibel or more). Thus in most cases it seems that with the years there is a progressive loss of hearing It should be pointed out that 4 patients have had a similar degree of hearing loss in the other ear without, however any symptoms of Ménière's disease elicited from this ear

At speech audiometry a considerable loss of discrimination was ascertained in most cases (in 14 patients the DL was 50 % or more) — and it was often increased when the test was performed with conventional hearing aid

That even a functionally poor hearing may be of importance appears from the following example: A patient who had previously undergone electrocoagulation a.m. Day of one ear owing to severe Ménière attacks, later suffered renewed attacks of vertigo elicited from the other ear. Vestibular section was therefore performed on the latter side. In spite of a discrimination loss of 80 %, this patient can now use a hearing aid with benefit in quiet surroundings when speaking to somebody alone. Under less favourable conditions the noise interferes. 6 other patients have tried to use a hearing aid but only one has derived any benefit from it. It is, however, possible that these patients might benefit from aids with automatic volume control (peak clipping), more particularly if the non-operated ear should become affected by a higher degree of hearing loss.

In 2 patients the follow-up examination showed that recruitment as determined by Fowler's test and by stapedius reflex threshold has disappeared after the operation. Finally a pronounced tone decay was found post-operatively in 7 patients.

6 patients were not followed up. Two of these had died from other causes several years after the operation. From 4 patients there was no response to the requests for follow-up examinations. It has, however, been verified that also these patients had been relieved of their attacks of gyratory vertigo.

Complications

Post-operatively 2 patients had a slight, temporary facial paralysis of about two months' duration.

Conclusion

Total or partial (vestibularis) section of nervus octavus permanently relieves the patient of incapacitating attacks of gyratory vertigo.

By total section there is in addition a great chance of relieving the patient of tinnitus, more so than by vestibular section only.

By vestibular section it is possible to preserve the hearing. The functional value of the residual hearing is rather small owing to poor discrimination. However, our material has shown that such functionally poor hearing may nevertheless give the patient a fairly good acoustic contact with his surroundings.

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VESTIBULAR PROBLEMS IN SPACE TRAVEL

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A short survey is made of the vestibular problems related to space travel i.e. 1) linear acceleration, 2) weightlessness and 3) rotating space stations. Longer periods of weightlessness make it necessary to generate artificial gravitation by rotation. The effects of coriolis acceleration in rotating environment have been studied and methods to overcome this disturbing fenomenon outlined.

One of the principal aims of space research in the USSR and the USA is, as is well known, to land the first man on the moon. The time when this will happen is coming nearer and nearer. The Russian moon-program is a well-kept secret, but the American program is more open to the general public, and can, in fact, be studied in detail by anyone. It envisages a manned landing on the moon before the end of the 1960s, and hence there are only 4 years to go. The extensive activities in space medicine that have been, and are still being, carried out parallel with intensive technical work are well-known, especially from American sources.

Among the problems of space medicine, studies on the function of the sense of equilibrium occupy a central position. In space travel astronauts and cosmonauts are exposed to peculiar stimulations of their organs of equilibrium, which can result in motion sickness, with nausea, vomiting and reduction of capacity.

Problems connected with the sense of equilibrium in space may be divided into three main groups: 1) strong linear acceleration, 2) weightlessness, 3) problems associated with rotating space stations. The first problem, had, to a great extent, been solved before the beginning of the space age in 1957 by studies in aviation medicine, especially with regard to the function of the circulatory apparatus, the testing of space suits etc. The studies were carried out with the aid of »human» centrifuges and linear acceleration tracks in a horizontal plane. This made it possible to presuppose the consequences of the linear accelerations and retardations, which on acceleration from the earth acquire a value of 7—8 g, and on re-entering the atmosphere a value of 7—10 g. It was known exactly how long a human being could stand such a great increase in g, and how this increase could be prevented by placing the astronaut in a suitable position, lying on his back with legs somewhat raised and head slightly elevated in order to obtain an adequate accumulation of blood in the brain and the immediate circulatory apparatus. It was found that these problems could be satisfactorily studied in large centrifuges for human beings in which the astronauts adjustable chairs were put.

Some problems concerned with the sense of equilibrium are not due to linear acceleration as such, even if some misinformation occurs. When there is very great acceleration in a horizontal plane, such as a modern jet plane can produce, the pilot has a sensation of rising upwards and forwards. On breaking, he has a similar sensation of falling forwards and downwards. This is a typical example of misinformation or illusion, due to unusual stimulation of the apparatus of equilibrium.

It has also been ascertained, by means of studies on experimental animals, that the otolithic apparatus itself, the sensory organ for linear acceleration, is not damaged by prolonged exposure to 10 g. Different studies have been made on monkeys after centrifugation in large centrifuges. The ability to become adapted to heavy g loads and readapted to 1 g made it possible to assume that also adaptation to values of linear acceleration (gravitational acceleration) under 1 g, i.e. less than on the earth's surface, could not cause any particular difficulties.

The second problem, the question of weightlessness, on the other hand was disquieting and caused much discussion, especially before the space flights which have now been accomplished. This was mainly because it is impossible to carry out really consistent terrestrial experiments for long periods. However, on the whole, three methods have been applied for studying weightlessness. One of these was to let an aeroplane fly in a so-called trajectory. In this way periods of weightlessness can be obtained, which usually last for 15—30 seconds, depending upon the type of aircraft and the manner of flight.

In the USA there are, for example, special aeroplanes and personnel that are used in medical and technical experiments in weightlessness conducted on behalf of the National Aeronautics and Space Administration (NASA). A regular type of passenger aeroplane is used for this purpose, where all the chairs etc are removed and the entire cabin padded on the inside, so as to prevent injuries when persons are freely occupying it during an experiment in weightlessness. Unfortunately these experiments in trajectory have the disadvantage that weightlessness lasts so short a time and, moreover, that just before weightlessness, a high g value is reached, namely 2 g. The aeroplane must, so to say, take a run before it flies in a trajectory, and after the trajectory there is a motion during which 2 g is again reached. This means that all the procedures of adjustment in the body that are affected during the trajectory, for example, the circulatory apparatus, and the apparatus of equilibrium which have latent periods of 30—120 seconds, cannot be regarded as satisfactorily studied.

Another method of studying weightlessness is free fall. Air resistance, however, soon changes the condition of actual weightlessness. Immersion in water is another method that has been extensively applied. In these experiments the body, which is provided with an oxygen system for breathing, is allowed to float about in a tank, or the body is immersed and the head remains above the surface of the water in prolonged experiments, for example, in studies on decalcification of the skeleton and reduction in strength of the body musculature, and in the study of certain psychological problems. For example, the diminished need for sleep has been studied in such experiments.

Unfortunately, immersion in water still has an effect on the otolithic apparatus, and this means that also in these cases the experiments are not genuine studies in weightlessness. Subjects without a labyrinthine function have also been used in such experiments in tanks. These experiments, however, are not studies in weightlessness in normal persons.

The space flights that have already been made, showed, however, that weightlessness in itself is not of any special significance for a trained astronaut.

It is interesting that the Russians have reported disturbances in one of their cosmonauts, Titov who suffered from vertigo as soon as he moved his head under conditions of weightlessness. The trouble caused by his equilibrium disturbance was clearly very considerable and might have involved an element of danger The Russians denied that the capsule rotated, otherwise his vertigo could have been explained by what is known as the coriolis effect The Russian three-man flight last year was interrupted earlier than planned because two of the men the engineer and the physician, suffered from such severe equilibrium disturbance that this jeopardized the whole experiment. The Russians are not entirely clear about the facts, but this is at present the American interpretation The Americans have not reported any serious disturbances in equilibrium. On the other hand, considerable misinformation and illusions have occurred These can be more curious than directly dangerous from a medical point of view For example, when the astronaut comes into orbit after great acceleration during the first seconds of weightlessness he has an intense sensation of standing on his head. He has also persistent hyperemia in the upper part of his body These sensations and symptoms recede, however comparatively soon.

Taken together this would perhaps imply an increased risk of equilibrium disturbance as soon as astronauts are not recruited from pilots, i e. from groups trained against equilibrium disturbance. Improved methods of selection and, possibly training programs are probably the expedients that will have to be chosen when it is no longer a question of employing highly experienced pilots.

Finally the third problem — the problem of equilibrium on rotating space stations — is of significant interest from many points of view The reason why rotation is aimed at is the desire to create, by means of centrifugal force »artificial gravity» which can counteract the great disadvantages of staying in space during a state of weightlessness. On a rotating space station the human body can retain its adaptation to terrestrial conditions; thus, for example, the expected enervation of the skeletal and heart musculature and the decalcification of the skeleton as a consequence of prolonged weightlessness, may be avoided. The circulatory system retains its adaptation to the body s erect position under gravity Finally the work at the station is facilitated with regard to locomotion, repair of apparatus, preparation and intake of food etc.

Staying in a rotating room, however creates special problems connected with the sense of equilibrium owing to what is known as coriolis acceleration. A physical law which, expressed in a simplified form, states that when a body moves along the radius during rotation, it is subjected to a tangentially directed linear force, which, on decreasing the radius, has the same direction as that of the rotatory motion, and which increases the rotation of the body

This force stimulates the body s static receptors, i.e. the otolithic organs and the pressure receptors in the joints and muscles. What should be observed, however is that when the head is moved it can also affect the cupula organ in the semicircular canals. This is due to the fact that when the head is turned the radius to the center of rotation is retained for those portions of the internal fluid of the labyrinth which cut the torsional axis in the plane of rotation. In the remaining

parts of the semicircular canals, however there occurs an increase or decrease in the radius to the center of rotation with the accompanying effect of coriolis acceleration. That such a flow takes place has been shown by Johnson in Toronto in a model experiment with a ring-shaped glass tube filled with liquid in which particles were floating On turning the ring with the liquid in a rotating room the liquid began to flow Thus, on turning the head during rotation there is simultaneous stimulation of the otolithic organs and the semicircular organs. The strength of the stimulus depends only upon the velocity of rotation of the room and the velocity of the shift along the radius, i.e the speed at which the head is turned. The strength of the stimulus is independent of the distance from the center of rotation.

Head movements during rotation cause, for movements typical of man, bending down, turning the head etc., already at a low speed of rotation of 2—3 revolutions per minute a surprisingly strong vestibular stimulation. The room appears to tilt, nystagmus — mainly vertical — can be observed, and after a few movements of the head, nausea occurs.

This effect of rotation causing motion sickness, is in many ways comparable with the equilibrium disturbance experienced in other vehicles. The essential solution of the problem is, that before astronauts are sent to the space stations they should train in rotation, with the direction and velocity of rotation which will be used, and, preferably also in the same position as on the rotating space-stations, i.e with the longitudinal axis of the body in a radial direction, with the head towards the center The magnitude of the coriolis acceleration is the same on earth as during rotation in space. The difference is, however that the resultant of the centrifugal force, coriolis force and gravity has a different direction from that of the resultant force in a space station, where only the resultant of centrifugal force and coriolis force is operative. Adaptation to a rotating room shows that good adaptation can be acquired in from 1 to 5 days when the velocity of rotation is between 1 and 10 revolutions per minute.

The adaptation of the system of equilibrium has proved, however to be very specific Here, the direction of rotation and also the velocity of rotation are important. During a prolonged stay in a rotating room there is a successive loss of adaptation to »nonrotation» even if the memory of our usual condition of »nonrotation makes the problem of readaptation comparatively easy and rapidly solved After a longer time, 2—3 months, under constant rotation, it is, to all appearances, nonetheless necessary from time to time to refresh the memory by a stay where there is nonrotation. This could be done by having in the center of a space station, a smaller room (on the same central axis as the large station) for counterrotation of the same velocity Thus, while staying in this room the resultant rotation would be 0 Moreover there would be condition of weightlessness in this room.

Head movement could, for example be practised once a day possibly combined with the training of other movements, in order to maintain physical tonicity By means of such training an astronaut could be prepared for transfer from a rotating space station to a smaller space capsule, in order either to return to

the earth or to continue flights into outer space. In the rotating space stations, which are at present being planned by the USA, such a room for counterrotation is included. Experiments on staying in a rotating room have yielded interesting insights into vestibular habituation. These problems are closely linked with clinical vestibular problems. For instance, habituation to one-sided destruction of the labyrinth. It is possible, and also highly appropriate, to divide the problems on habituation to a rotating room into a number of special problems, a procedure which has been adopted. The system for the sense of equilibrium when regarded as a whole, seems, however to be extremely complex. There are also substantial experimental difficulties. Nonetheless, the ideal astronaut is not a being without a vestibular function, but a being who is well habituated to the unusual stimuli he is exposed to. There is every indication that man will succeed also in solving this part of the problems connected with space flights.

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CALORIC REACTION IN MENIÈRE'S DISEASE

A NYSTAGMOGRAPHIC STUDY OF 300 PATIENTS

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The caloric reaction was abnormal in 84% of the patients. In 65% of all patients the caloric response was reduced. A combination of reduced excitability and directional preponderance was a common finding. The disease was found bilateral in 14%. After 10 years of disease this frequency was raised to 25%. Both the caloric response and the hearing seemed t deteriorat mainly dur ing th initial years.

The caloric reaction can make an important contribution not only to the diagnosis of Menière s disease but also in assessing the extent of the labyrinthine involvement. Electronystagmographic recordings (ENG) adds to the accuracy in permitting the use of several parameters instead of only duration.

The caloric reaction yields four types of response 1 reduced excitability (= canal paresis), 2 directional preponderance, 3 combination of reduced excitability and directional preponderance (= combined lesion), and 4 normal response

A review of some great case materials reveals, that Cawthorne & Hewlett (1954) amongst 900 patients with severe Menière s disease have noticed an abnormal caloric reaction in 95 %. Of these 71 % revealed a reduced excitability Castellano (1958) on the other hand, who has performed a follow-up investigation of 500 patients treated by Olivecrona, has reported reduced caloric response in only 57 %. These two groups were investigated without nystagmography

During the last 5—6 years a great number of Menière s patients have been investigated at the Ear clinic in Uppsala, most of them in connection with selection for ultrasonic irradiation therapy Our results are based on 300 consecutive cases, of whom 180 were later operated.

The disease was unilateral in 258 and bilateral in 42 (= 14%). These figures are in agreement with other reported studies. However it should be mentioned, that a higher frequency of bilateral involvement has been reported by Ophelm 1963 (20 %) and Wright 1948 (28%) The number of bilateral cases increases with the duration of the disease. *After 10 years or more no less than 25% showed bilateral impairment* — a fact which should be considered when deciding on treatment.

Menière s disease strikes men more often than women (55 and 45 respectively) — a ratio which is almost the same for all larger series.

A detailed analysis of the nystagmographic recordings of the caloric reaction revealed a normal response in 49 patients (16%) and an abnormal response in 251

[1]) This work was supported by the Swedish Medical Research Council (Project No. 17 X—617—01).

(84 %). Among the 251 patients with abnormal reactions the distribution was as follows: 153 reduced excitability, 76 directional preponderance and 22 hyperexcitability, which means a stronger reaction from the diseased inner ear as compared with the healthy side.

Two points are of special interest. 1. The frequency of abnormal reactions does not increase with a longer duration of illness. This might indicate that the labyrinth gets permanently damaged early. 2. A stronger response from the diseased side can sometimes be elicited.

The intensity of the caloric response seems to be a more reliable parameter than the duration in evaluating the labyrinthine function. The intensity can be expressed in different ways — the speed of the eye according to Henriksson 1956, the total number of beats, or the total amplitude of all nystagmus beats. Suitable for clinical work is the recording of the mean eye speed in the slow nystagmus phase at the peak of the reaction (Stahle 1956, 1958, Stahle & Sahl, 1963). We have termed this as the »maximum intensity».

A comparison between duration and maximum intensity revealed that abnormal durations have been registered in 197 patients (66 %) and abnormal maximum intensities in 219 patients (73 %). An estimation of the maximum intensity alone thus revealed some more cases with abnormal reactions than if the estimation should be based on duration. *If both parameters are used together the total amount of patients with an abnormal response will be 251 (84 %).* These figures prove that ENG increases the possibilities for diagnosing an inner ear lesion.

It has been discussed in the literature if the direction of the preponderance is of any importance for deciding what side is the diseased one. Our cases show a preponderance from the diseased ear in 58 % and towards the diseased ear in 42 % of the total material. In relation to time, however, a preponderance from the diseased ear seems to be more common in recent cases and towards in more long-standing cases. In accordance with Koch, Henriksson and co-workers 1959 we have come to the conclusion that the direction of the preponderance gives no information of the site of the lesion.

In addition an investigation was performed on the influence of time upon both the caloric response and the hearing. It was found that with time the caloric response and the hearing progressively diminished. In regard to the caloric reaction the intensity was reduced more than the duration. This fact has strengthened our opinion that the intensity of the response is a more sensitive indicator than the duration.

The reduction of the vestibular function seemed to take place during an early phase of the disease. In a group of 90 patients with a history of illness not exceeding 3 years, the mean values for maximum intensity had diminished 35 %, while duration was shortened only 18 %. In the same group the mean pure tone audiogram revealed a 49 dB hearing loss. In another group of 77 patients with an illness lasting 10 years or more the mean value was 57 dB.

Our result seem to indicate that cochlear function is reduced more than the vestibular — a result in full accordance with the general opinion of the greater

vulnerability of the cochlea. Noteworthy is the fact that hearing was greatly reduced early in the disease.

Thus we feel strongly that active therapy should be started early in an attempt to stop a progression of the disease. We therefore follow earlier presented principles including initial medical treatment with diuretics etc., followed in intractable cases by surgical treatment with ultrasonic irradiation of the vestibular part of the inner ear.

An extensive report on the material including tables will be published in the *Laryngoscope* 1967.

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A SIMPLE AND INEXPENSIVE APPARATUS FOR CALORIC STIMULATION OF THE EAR

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An »inexpensive thermostat for the Hallpike test» was described by Mc Govern in the January number of Archives of Otolaryngology Vol. 83, 1966. At the time, we already had at the Central Military Hospital in Helsinki, an apparatus for the same purpose which probably is even less expensive and easier to procure.

This apparatus, fitted at our own hospital, cost about one tenth of the price at which the hospital had been offered an apparatus, specially constructed for the same purpose

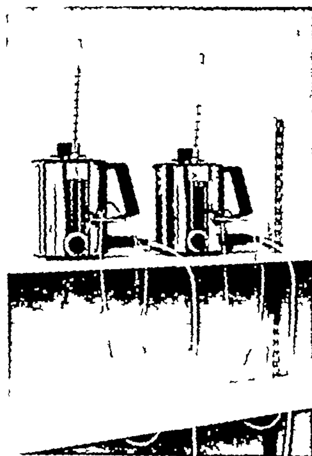


Fig. 1 Two thermostat-regulated electric heaters (Braun HE 1), each equipped with an outlet having provision for closure Attached to the outlet is a polyethylene tube (Portex 6 H), which is inserted, without a nozzle into the auditory canal.

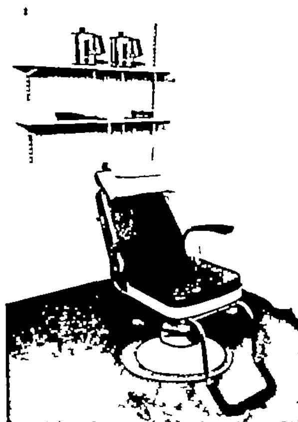


Fig. 2. The equipment combined with an adjustable chair (Pfa 6850), which ca also be used for th rotation test.

The equipment is illustrated in figure 1 Figure 2 shows the same apparatus combined with a suitable examination chair

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CALORIC TEST WITH AIR

PRELIMINARY REPORT

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(Head. Prof. Otto H. Meurman, M.D.)

The author has constructed a thermoregulable air blow apparatus, by which a caloric test can be performed. As subjects have been used persons with normal ears and patients with perforations in the tympanic membrane. The results have been compared with the usual caloric tests after Hallpike made by cold and warm water. The results show that a caloric test reliably can be made by air. Special attention is paid to different error possibilities.

Everywhere in the world the caloric test has become a common part of the oto-neurologic examination, particularly because of the fact that it is simple to carry out and gives quite reliable results. Merely with its help it is possible to get a quite fargoing differential diagnosis between peripheric and central vestibular disturbances (Hallpike 1942, Aschan 1964, Ledoux 1966). As a further advantage of the caloric test can be mentioned that each labyrinth can be examined separately; in the rotatory test one always get as result the summation of both labyrinths. When the test circumstances are suitable standardized, tests done in different clinics are comparable. By a dry perforation of the tympanic membrane the caloric test with water is, however, absolutely contraindicated. If the ear is discharging, water irrigation can be done, if normal thermostate water is avoided. Very often it is not steril.

To patients, who have dry perforations, caloric tests have been done either by blowing air, ether or ethylene chloride (Frenzel 1944, Meurman & Pursiainen 1952, Philipszoon 1960). However, quantitative results have not been reached by these examinations. Mittermaier (1965) for instance is of the opinion that by blowing air quantitative results are not even to be expected. It is evident that quantitative results cannot be received by injecting ether or ethylene chlorid into the ear or by placing cotton, saturated with these liquids, into the auditory canal. Naturally it is not possible to do a test with those according to Hallpike, too. For the present, blowing of air into the ear has been limited, because there have been no such measuring instruments available, with which both the quantity of air blown into the ear and especially its temperature accurately enough could have been measured.

The industries, however, have at their disposal thermoanemometers, with which both the temperature of air and its flow speed accurately enough can be measured. With such a measuring instrument the temperature of air blown into the ear can be measured at least with 0.5° exactness, and the flow rapidity of air with 1 m/sec. This exactness combined with a suitable air blowing apparatus

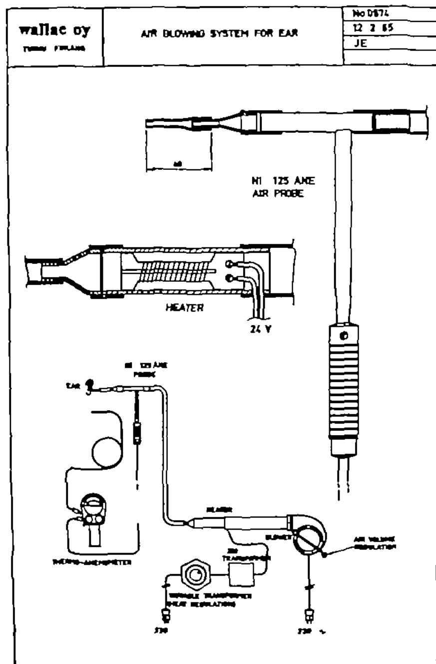


Fig. 1

and a heating device is already a satisfactory condition for carrying out the caloric test quantitatively according to Hallpike Fig 1 shows the equipment which is co-operately constructed by an industry in Turku, Wallac Oy which produces electric measuring instruments. The motor of the blower is a quite simple electric 65 W one The flow of air is directed through the heating device to

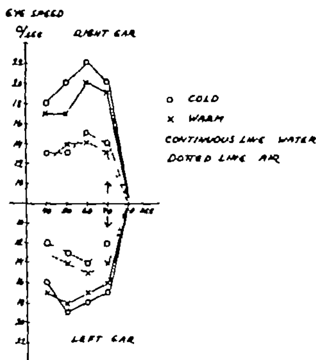


FIG 2

the set of equipment, and with its help the flow of air can be blown into the ear towards the posterior osseous wall of the auditory canal, which is considered to be the optimal point for the rising of the caloric reaction (Dohlman 1925). The tip to be pushed into the ear is a 3.5 mm thick soft plastic tube, (which does not cause pains even when it comes in contact with the walls of the auditory canal especially when the edges of the nib are curved) Air is blown through the set of equipment about 12 m/sec., which corresponds to about 1.2 l/min.

The temperature of air to be blown into the ear is regulated, so that at a distance of 0 75 cm from the tip of the plastic tube it corresponds to the water temperatures of 30 and 44 in the Hallpike test

Compared with Aschan s (1955) experiments, where he proves that already ½ degree s difference in the temperatures of the water could bring about remark able differences in the results, 0.5 exactness seems to be very small in theory In practice, however when the tests done with water and with air according to the described system, are compared, it seems, as if the exactness were enough for clinical work at least when done by person acquainted with the method.

A narrow auditory canal or big anatomical differences for example operation cavities can give wrong results in the caloric test with water These sources of error also exist when test with air is done. Moreover it is to be observed that water evaporated from a moist auditory canal, because of blowing, binds heat, and may give a wrong result. Under such circumstances the blowing test is not to be done till the auditory canal is dryed. A perforation in the tympanic membrane can also give a wrong result, especially if the perforation is large. This can be avoided by

ngly favour the opinion that in the region of the the statoconium membrane lies closer to the sensory rystal masses on either side. The inferior surface of the macula utriculi in the region of the striola on the concave and thus further away from the sensory

rs from less than 1 μ to almost 50 μ in the guinea pig, but constant The largest crystals lie in the basal lanes above the lateral region of the macula utriculi f the macula sacculi. Smaller crystals are found in ost marginal layers of the statoconium membranes. ell has a single kinocilium and 70—100 stereocilia. t the periphery of its associated bundle of stereocilia. f the bundle as a whole determines the morphological amining a surface specimen it is not only possible to lium relative to that of the stereocilia, but also the surface of the epithelium as a whole (fig 1)



h showing hairbundles t the surface of the sensory me side of the hairbundles (arrows). 1560 ×

d Wersäll, the hairbundles of each crista me direction. The sensory cells of the crista loser to the utriculus than their associated cells on the cristae posterior et superiores from the utriculus than their associated

CELLULAR PATTERN AND NERVE SUPPLY OF THE VESTIBULAR SENSORY EPITHELIA

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This paper is a short survey of a more comprehensive work on morphological studies carried out on the vestibular sensory regions. The surface specimen technique used by Engström has been applied in these studies. This method allows of an exellent view of the vestibular sensory epithelia as a whole or in part.

The membranous labyrinth after fixation is prepared free under the stereo-microscope and may be studied in detail The three ampullae, the utricle and the saccule are opened and the cupulae covering the sensory epithelia of the cristae and the statoconium-membranes covering the maculae are removed The sensory epithelia in their entirety are then peeled off the underlying tissues and may be further studied by both light and phase contrast microscopy By means of focusing the microscope at different levels one can obtain »optical sections» wherein lie in turn, the hairs, the free cell surface and the nuclei of both sensory and supporting cells.

Blood vessels and nerves within the sub-epithelial tissues can similarly be studied

The membranes covering the maculae in mammals consist of a large number of crystals — statoconia — embedded in a gelatinous substance. These statoconium membranes show regional differences in the size of the crystals, thickness of the membrane as a whole as well as in the thickness of the gelatinous substance enveloping the crystals. Werner called this substance »das Macularium» On each macula he found regions where the macularium was thicker and which at times stained well with hematoxylin This thickened zone of the macularium he called the striola As a matter of fact the crystal layer lying above, as well as the sensory epithelia lying below this zone of the macularium show a rather special regional construction. The striola here defines the position of these particular regions on both statoconium membranes and sensory epithelia

It has long been known that there exists in the statoconium membrane of the macula sacculi a snowdrift-like thickening running along its middle and which is now known to correspond to the striola However no such thickening is present in the striola of the statoconium membrane of the macula utriculi. Further it has been shown and proved by means of microradiographic studies that the crystal layer in the striola here is considerably thinner than on either side The statoconium membrane of the macula utriculi also shows numerous small depressions which on microradiography appear as craters. These are generally found in the striola

This study has been supported by grants from U S. Office of Naval Research (Contract No. N62558-4261 with H. Engström)

Repeated observations strongly favour the opinion that in the region of the striola of the macula sacculi, the statoconium membrane lies closer to the sensory epithelium below than do the crystal masses on either side. The inferior surface of the statoconium membrane of the macula utriculi in the region of the striola on the other hand, appears slightly concave and thus further away from the sensory epithelium below

The size of the crystals differs from less than 1 μ to almost 50 μ in the guinea pig, their distribution is uneven but constant. The largest crystals lie in the basal part of the statoconium membranes above the lateral region of the macula utriculi and the antero-inferior part of the macula sacculi. Smaller crystals are found in the striola and in the uppermost marginal layers of the statoconium membranes.

Every vestibular sensory cell has a single kinocilium and 70—100 stereocilia. The kinocilium usually lies at the periphery of its associated bundle of stereocilia. Its relative position to that of the bundle as a whole determines the morphological polarization of the cell. By examining a surface specimen it is not only possible to note the position of the kinocilium relative to that of the stereocilia, but also the relationship of these to the surface of the epithelium as a whole (fig. 1)



Fig. 1 Surface specimen of macula sacculi showing hairbundles at the surface of the sensory cells. Kinocilia on one and the same side of the hairbundles (arrows). 1500 ×

As described by Lowenstein and Wersäll, the hairbundles of each crista ampullaris are all oriented in the same direction. The sensory cells of the crista lateralis have their kinocilia lying closer to the utriculus than their associated bundle of stereocilia, whereas sensory cells on the cristae posterior et superiores have their kinocilia lying further away from the utriculus than their associated bundle of stereocilia.

Although the hairbundles on a crista are all oriented in the same direction is is not so in the case of the maculae Engström, Flock and Spoendlin have dependently shown that each macula is divided by an arbitrary curved line into vo areas. In the macula utriculi the kinocilia on the sensory cells in either area e nearer the curved line than their associated bundles of stereocilia, whereas on ie macula sacculi the reverse holds. The so called curved line has in fact a slight avy configuration.

By observations made on guinea pigs and other animals the position of the irved line was found to be constant and may be anatomically defined to lie along ie middle of the striola It was further observed that at either end of the striola 1 both maculae, the sensory cells show divergences in their morphological olarization.

Whereas in the guinea pig the bundle of stereocilia on the sensory cells of the hole macula sacculi are closer to the curved line than their associated kinocilia, iere exists, however in the cat a marginal area of sensory cells along the anteroiferior border of this macula, whose bundles of sterocilia lie further away from ie said curved line than their associated kinocilia.

The kinocilium, in the maculae at least, is a much longer structure than the ingest stereocilium, and also more flexible than its associated stereocilia. Because f this, the distal end of the kinocilium may assume any position above the cellular irface. Its true position however may be determined by locating it at the cell irface. It can thus be appreciated how a section taken at any level other than at he cell surface may give an erroneous impression of the relative position of the inocilium and hence fallacies in determining cell polarization. In a surface pecimen the distal end of the kinocilium in whatever position it might lie above he cellular surface may be identified and the kinocilium followed along its entire ength to its origin on the cell surface simply by focussing down on to various optical lanes.

The vestibular sensory epithelia are formed by a single layer of cells consisting f both sensory and supporting elements. Whereas all elements reach the free pithelial surface, the supporting cells alone rest on the basement membrane. The uclei of the supporting cells are normally found to lie in a zone in the most basal art of the epithelium, whereas those of the sensory cells lie at varying levels bove them. As described by Werner this was found to be most constant and onspicious in the striola of the maculae. In the more peripheral parts of the pithelium however zonal differentiation was less obvious. In a surface specimen he two distinct zones of sensory and supporting cell nuclei in the striola may be iewed simply by focussing and thus altering the optical plane of the light microcope. It was interesting to note that in the optical plane where the nuclei of the upporting cells are in view there exist in the striola, particularly in that of the nacula utriculi, a number of fairly large, clear spaces. These are faintly recognized vhen viewed from a higher optical plane. See fig 2 and fig 3

By examining a surface specimen it was observed that in the striola of both naculae sacculi et utriculi, the sensory cells have a large free surface, whereas the urface of those cells on either side are considerably smaller (fig 4) The density of

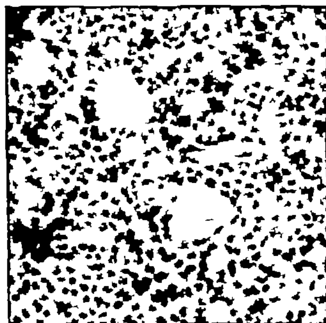


Fig. 2. Optical section in surface specimen of macula utriculi in region of striola. Nuclei of supporting cells in view. Note spaces referred to in text. 940×

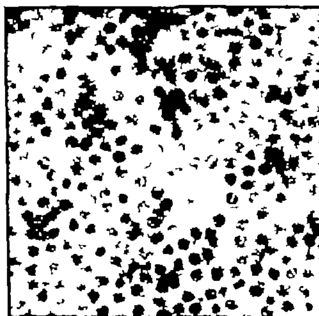


Fig. 3. Higher optical section than in fig. 2. Nuclei of sensory cells now in view. Spaces appear faint. 940×

sensory cells on the maculae varies in different regions. The number of sensory cells per surface area in the striola is less than that on either side of it. The average density of hair cells on the macula utriculi is slightly higher than that of the macula sacculi.

Although the hairbundles on a crista are all oriented in the same direction, this is not so in the case of the maculae. Engström, Flock and Spoendlin have independently shown that each macula is divided by an arbitrary curved line into two areas. In the macula utriculi the kinocilia on the sensory cells in either area are nearer the curved line than their associated bundles of stereocilia, whereas on the macula sacculi the reverse holds. The so called curved line has in fact a slight wavy configuration

By observations made on guinea pigs and other animals, the position of the curved line was found to be constant and may be anatomically defined to lie along the middle of the striola It was further observed that at either end of the striola on both maculae, the sensory cells show divergences in their morphological polarization.

Whereas in the guinea pig the bundle of stereocilia on the sensory cells of the whole macula sacculi are closer to the curved line than their associated kinocilia, there exists, however in the cat a marginal area of sensory cells along the antero-inferior border of this macula, whose bundles of sterocilia lie further away from the said curved line than their associated kinocilia.

The kinocilium, in the maculae at least, is a much longer structure than the longest stereocilium, and also more flexible than its associated stereocilia. Because of this, the distal end of the kinocilium may assume any position above the cellular surface. Its true position however may be determined by locating it at the cell surface It can thus be appreciated how a section taken at any level other than at the cell surface may give an erroneous impression of the relative position of the kinocilium and hence fallacies in determining cell polarization In a surface specimen the distal end of the kinocilium in whatever position it might lie above the cellular surface may be identified and the kinocilium followed along its entire length to its origin on the cell surface simply by focussing down on to various optical planes.

The vestibular sensory epithelia are formed by a single layer of cells consisting of both sensory and supporting elements. Whereas all elements reach the free epithelial surface, the supporting cells alone rest on the basement membrane. The nuclei of the supporting cells are normally found to lie in a zone in the most basal part of the epithelium whereas those of the sensory cells lie at varying levels above them. As described by Werner this was found to be most constant and conspicious in the striola of the maculae. In the more peripheral parts of the epithelium however zonal differentiation was less obvious. In a surface specimen the two distinct zones of sensory and supporting cell nuclei in the striola may be viewed simply by focussing and thus altering the optical plane of the light microscope It was interesting to note that in the optical plane where the nuclei of the supporting cells are in view there exist in the striola particularly in that of the macula utriculi, a number of fairly large, clear spaces. These are faintly recognized when viewed from a higher optical plane See fig 2 and fig. 3

By examining a surface specimen it was observed that in the striola of both maculae sacculi et utriculi, the sensory cells have a large free surface, whereas the surface of those cells on either side are considerably smaller (fig 4) The density of

bear a much smaller free surface (fig. 5) The numbers of cells are the same in comparable regions of a crista. In general, the demarcation line between the vestibular sensory epithelia and surrounding areas is rather distinct. In certain regions however this zone is transitional and sensory cells are sparsely scattered within groups of supporting cells.

The distribution of the supporting cells shows clear regional variations. On the maculae the supporting cells in and around the striola are more numerous per surface area than peripherally

The supporting cells contain osmiophilic granules. In the striola and in the central regions of the cristae, the granules in these cells are larger and more numerous than those in the periphery

Quantitative observations of sensory and supporting cells can be carried out in different ways; by counting the hairbundles of the sensory cells, by counting the sensory and supporting cells at a level with the reticular membrane or by counting their nuclei. Counts of sensory cells were made in different regions and the surface area of the entire macula and crista determined The approximate total number of sensory cells in the various vestibular sensory epithelia in the guinea pig are as follows, macula sacculi 6 000 macula utriculi 8 400 crista lateralis, 6 000

	Surface area	Approximate number of sensory cells
Macula sacculi	0,48 mm^2	6900
Macula utriculi	0,55 mm	8400
Crista lateralis	0,40 mm^2	6000

Wersäll has described two different types of vestibular sensory cells — type I and type II Type I is flask shaped and type II is cylindrical. In an optical plane corresponding to the epithelial surface the type I cells in the striola and in the central parts of the cristae generally have a larger free surface area and appear more distinct than the type II cells elsewhere the two types of cells can hardly be differentiated. The type I cell is however surrounded by a nerve chalice rich in mitochondria In surface specimens fixed in osmic acid, the nerve chalice appears as a dark ring and thus indirectly allows identification of the type I cells (fig 6). It is not uncommon to find 2—4 type I cells within a common large nerve chalice. This is particularly conspicious in the striola The number of type I cells per surface area, in the periphery is greater than that in the more central parts of the crista Around 60% of the sensory cells in the central areas as well as in the periphery constitute the type I cells. There are about twise as many cells of type I as those of type II in the striola of the maculae, whereas in the periphery these have a more or less equal distribution.

As pointed out by Cajal, Lorente de Nó Poljak and Wersäll, the central parts of the cristae are supplied with especially thick nerve fibers, whereas the fibers in the periphery are less thick. Lorente de Nó showed that on the macula utriculi there are also regional differences in the distribution of thick and thin fibers.

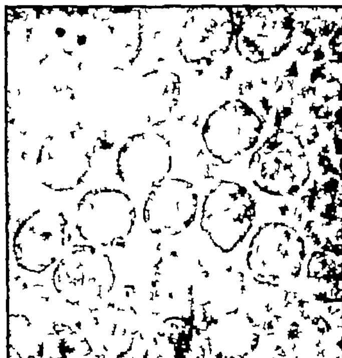


Fig. 6. Surface specimen of crista ampullaris. Nerve chalices containing mitochondria surround type I cells and ppear as dark rings. 1560 ×

Studies made on surface specimens show that very thick myelinated fibers run to the striola of the macula utriculi, these fibers appear to penetrate the basement membrane more perpendicularly than those on either side. Very thick fibers run to the anterior part of the striola of the macula sacculi, whereas these are not so conspicious along the rest of the striola.

Sensory cells in the more peripheral parts of the maculae are supplied by nerves having a longer intra-epithelial course.

The macula sacculi is innervated by nerve fibers from pars superior and pars inferior of the vestibular nerve. According to Poljak and others these two areas are fairly separately innervated In surface specimens it was however seen that fibers from the two branches show a clear overlapping

In the guinea pig it can further be observed that myelinated fibers coming from the pars superior of the vestibular nerve are running into the area supplied by the pars inferior These run lengthwise in the macula sacculi (fig 7). The fibers are thin and constitute a constant finding

The sensory cells of the vestibular sensory epithelia are innervated by afferent and probably also efferent nerves. Throughout their intra-epithelial course these fibers are unmyelinated The thicker nerve fibers run, after branching, to a relatively small number of type I cells and end around these cells with nerve chalices. The type II cells are supplied mainly by thin fibers, which form bud shaped terminals at the base of the cells. Concerning this innervation there is how ever as pointed out by Engstrom, a clear overlapping so that both type I cells and type II cells may be innervated by the same nerve fiber These fibers are

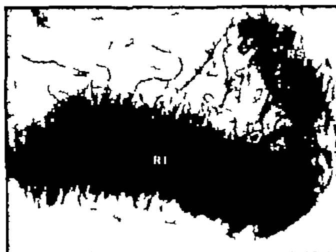


Fig. 7 Innervation f macula sacculi. Myelinated nerve fibers from pper (RS) and lower (RI) division of th vestibular nerve. N t the bundle f fibers running lengthwise in macula sacculi (arrow).

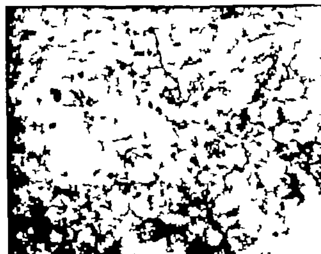


Fig. 8. Surface specimen of crista ampullaris showing the plexus of fine intra-epithelially running nerve fibers and their bud-shaped terminals. These fibers are probably of efferent nature. 910 X.

supposed to be of afferent nature. In addition, by electron microscopy granulated, probably efferent nerve terminals are found.

When studying the thin fibers, we have in this laboratory used a modification of a technique first described by Maillet, which in the cochlea fairly selectively stains the efferent fibers and their terminals. With the aid of this technique we have shown a rich plexus of fine fibers running at the base of the sensory cells, ending with bud-shaped nerve terminals on the nerve chalice of cells of type I, on the plasma membrane of type II cells and on the thicker intra-epithelially running nerve fibers.

It has been proposed to study the effect of antibiotics of the streptomyces group upon the vestibular sensory epithelia. The surface specimen technique is well suited for such studies and quantitative observations of the cellular damage are obtainable within few hours of sacrificing the animals.

One group of guinea pigs have had streptomycin injected intratympanically whilst another group have had kanamycin administered parenterally

Vestibular sensory epithelia obtained from these animals showed changes of the sensory cells, these include clumping of chromatin in the periphery of the nuclei, pyknotic nuclei, fragmented nuclei, hairbundle changes, cytoplasmic protrusions and »collapse-figures», indicating a complete degeneration of sensory cells.

The above changes are more noticeable in the cristae than in the maculae. Moreover the changes are more marked in the macula utriculi than in the macula sacculi.

These degenerative changes involved primarily the sensory cells in the central areas of the cristae and those in the striola of the maculae. In these regions the sensory cells thus appear to be more vulnerable to streptomycin and kanamycin than those cells in the periphery

It may also be added that the type I cells appear to be more sensitive to damage than the type II cells.

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QUANTITATIVE BIOCHEMICAL CHANGES IN SINGLE NERVE CELLS OF THE VESTIBULAR SYSTEM AT DIFFERENT FUNCTIONAL STATES.

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As parameters of functional level using quantitative methods total amount of RNA and succinooxidase activity have been measured in singl dissected o t cells from th lateral vestibular nucleus and from different areas of cerebellar cortex in rabbit. Bilateral samples have been analyzed after section of the vestibular nerve on the right side, after unspecific vestibular stimulation and after repeated calorization with warm and cold water Th results sh w it is possibl to demonstrate dysbalance in the vestibular system in biochemical terms and that a change f the functional state on one sid influences th functional state f the sam structures on th other side.

The knowledge we have today about the vestibular system is above all gained by works of neurophysiologists and morphologic studies. In spite of the imposing research work which has been made in these respects during the last decades we have to face the fact that our knowledge is crude. When one is concerned in clinical analyses of vestibular cases our methods are loaded with errors both for functional and topical diagnostic work.

A series of methods for quantitative biochemical analyses of single nerve cells has been developed at the department of neurobiology in Göteborg (Hydén and Pigon, 1960) With the aid of these, it is possible to express in biochemical terms the different functional states in the nervous system. The methods are not alter native but complementary to neurophysiology and morphology A number of investigations of this type on cell samples from the vestibular system has been published. (Hamberger and Hydén 1963, Hallén and Hamberger 1964 Blomstrand, Hallén, Hamberger and Jarlstedt 1966) Some examples of this work will be summerized here.

Methods

Principally two cytochemical parameters have been followed. The total amount of RNA per cell was measured by the method developed by Edström (Edström 1953) The activity of succinoxidase per cell was measured with Zeuthens micro-diver technique (Zeuthen 1953) applied for nerve cells by Hydén and Pigon (1960)

RNA determination

The tissue to be analysed was removed immediately after death and fixed in Carnoy s solution, embedded in paraffin and cut at 50 microns. Single nerve cells were isolated by micromanipulation from the sections and extracted with ribo-

nuclease in an oil chamber The extracts were collected, evaporated and redissolved in a glycerol-containing buffer forming lens-shaped drops. The ultraviolet absorption at 257 mμ was determined by a photometric system.

Succinoxidase activity determination

Under stereomicroscope fresh nerve cells were isolated and introduced into micro-divers with about 0.5 μl of incubation medium Oxygen consumption was determined manometrically for 2—3 hours and was expressed as 10^{-4} μl O_2 per sample and hour

Central compensation after unilateral vestibular neurotomy

Three groups of rabbits were subjected to right-sided vestibular neurotomy The animals of the first group were killed after operation, the others after 15 and 30 days respectively Bilateral samples of isolated large nerve cells from the lateral vestibular nucleus, were analyzed on total amount of RNA and succinoxidase activity Bilateral samples of Purkinje cells from lobulus III were analyzed on total amount of RNA. The results are illustrated in fig. 1 The RNA amount of

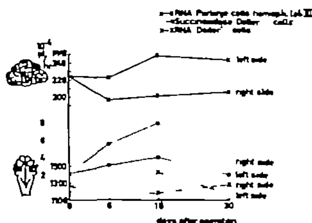


Fig. 1 Neurotomy N. VIII. right side. Summary of RNA and succinoxidase activity results: correlation of observations and time after operation.

Purkinje cells from lobulus III, hemisphere showed a significant side difference with lower values on the operated side. The difference already exists after one week, increases after two weeks and remains unaltered after four weeks. The cells from the nodulus show even higher side difference, but the cells from paraflocculus, which is not engaged in the vestibular system show no difference The RNA amount of the cells from the lateral vestibular nucleus shows no significant changes. The succinoxidase activity in the Deiters cells increased over 100 after two weeks on the operated side. After four weeks this difference has subsided. The results coincide with the central compensation. Hypothetically they can be an

expression for a hypersensitivity built up in the lateral vestibular nucleus of the operated side, a decreased inhibition from the cerebellar cortex of the same side and an increased inhibition from the other side.

Monolateral cold- and warmwater calorization

Four groups of rabbits were calorized in the left outer ear: the first and second with cold (20°C) and warm (48°C) water respectively for 30 minutes daily for seven days the third and fourth with a single 30 minutes warm and cold water irrigation,

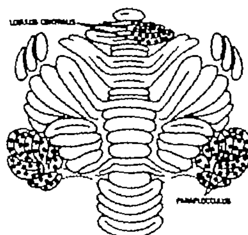


Fig. 2. Rabbit cerebellum unfolded in one plane. Surface view (Redrawn after Brodal 1940). Areas with unilaterally higher Purkinje cell RNA content after cold water irrigation in the left outer ear ●● Areas with bilaterally similar Purkinj cell RNA content after cold water irrigation in the left outer ear ○○

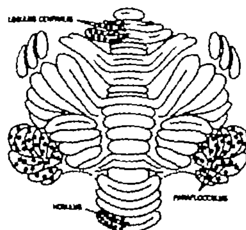


Fig. 3. Rabbit cerebellum unfolded in one plane. Surface view (Redrawn after Brodal 1940). Areas with unilaterally higher Purkinje cell RNA content after warm water irrigation in the left outer ear or after right-sided vestibular neurotomy ●●

Areas with bilaterally similar Purkinj cell RNA content after warm water irrigation in the left outer ear or after right-sided vestibular neurotomy ○○

respectively. After the last calorization the animals were killed. Bilateral samples of isolated cells from lateral vestibular nuclei were analyzed on total amount of RNA and succinoxidase activity. Bilateral samples of Purkinje cells from lobulus III hemisphere, were analyzed on total amount of RNA. In fig. 2 the influence of the cold water irrigated on the Purkinje cells is illustrated. The cells from lobulus III, hemisphere, contain significantly more RNA on the non-irrigated side, as well after repeated as after a single irrigation. The controls from the lobulus paramedianus and paraflocculus shown no side difference. The influence of warm water irrigation is illustrated in fig. 3. Here the result is the opposite with higher values on the left, i.e. the irrigated side. The RNA analyses from the lateral vestibular nuclei did not disclose any significant side difference. However the succinoxidase activity in the Deiters cells is clearly changed. After repeated cold water irrigation the values from the contralateral side increase around 100%. After repeated warm water calorization the values from the ipsilateral side increased about 60%. The animals irrigated once did not show any side difference. It is possible that the results are an expression for a decreased and increased afferent impulse flow respectively against the vestibular nuclei and cortical vestibular regions in the cerebellum. It is also possible that the changes of RNA content in the Purkinje cells mean a decreased respectively increased cerebellar inhibition. Finally the results may also be the biochemical correlate to the crossed labyrinth inhibition.

Conclusions

All kinds of hypothetic interpretation of the results excluded, the investigations here summerized can be said to document.

1. That it is possible to apply quantitative whole cells analyzes of RNA content and succinoxidase activity on samples from the cerebellar cortex and the lateral vestibular nuclei.
2. That the different functional situations in the vestibular system are disclosed by these parameters.
3. That a change of the afferent impulse flow from one of the labyrinths changes the functional state of the cells of the contralateral vestibular cerebellar cortex and lateral vestibular nucleus.

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MORBUS MENIÈRE — CEREBRAL ATROPHY

A PRELIMINARY REPORT

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From the University Hospital, Rikshospitalet, Oslo, the Department of Otorhinolaryngology (Head. Professor Peter Berdal, M.D.), the Department of Neurology (Head. Professor Sigvald Refsum, M.D.), and the Department of Radiology (Head. Professor Torleif Dal M.D.).

At Rikshospitalet in Oslo, 20 randomly selected patients with classical picture of Menière disease have been investigated. The results indicat that the tissue damage and functional disturbances giving rise to Menière's disease are not limited t the labyrinth alone but that the central nervous system is also the seat of *pathologic changes. Further investigations are being carried out.*

Clinically Morbus Menière is characterized by cochlear and vestibular symptoms. The aetiology and pathogenesis of the disease are unknown. Histologically how ever considerable dilatation of the endolymphatic apparatus has been demon strated (Hallpike and Cairns 1938 Hallpike and Wright 1940 Rollin 1940 Lindsay 1942, 1944 Altmann and Fowler 1943, Cawthorne 1947 Kristensen 1961 Schuknecht et al. 1962; Altmann and Kornfeldt 1965 and others). Because of these anatomic findings and the clinical picture Menière s disease has usually been regarded as a disease of the labyrinth (Ophelm and Flottorp 1957).

The observations of some research workers (Berggren, Aschan and Stahle 1957 Maspetiol et al. 1961 Hansen and Reske-Nilsen 1965) indicate that not only the labyrinth but the central nervous system as well contains pathologic changes. The object of the present study was to investigate this problem.

Material and methods

The material consisted of 20 at random selected patients with the classical picture of Menière s disease. They were studied in the following manner

1) Oto-rhino-laryngological investigations
2) Audiological investigations
3) Neurological investigations
4) Psychological investigations (16 patients)
5) Medical investigations
6) Ophthalmological investigations
7) Pneumoencephalography
8) Electroencephalography
9) Arcography (7 patients)
10) Vertebral angiography (5 patients)

When evaluating the pneumoencephalographical findings, the methods of measurement described by Engeset and Skraastad (1964) were employed (fig 1).

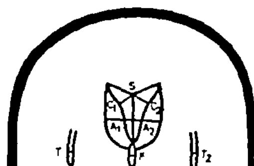


Figure 1 Engeset and Skraastad's method of measurement in pneumoencephalography: C_1—S or C_2—S pathologic at ≥ 15 mm A_1 or A_2 pathologic at ≥ 25 mm. F pathologic at ≥ 9 mm and T pathologic at ≥ 5 mm.

The age and sex distribution of the patients is shown in table 1 The duration of Menière's disease from the first symptom to the date of the investigation is shown in table 2.

TABLE 1

SEX AND AGE OF 20 PATIENTS SUFFERING FROM MENIÈRE'S DISEASE

Age (years)	Female	Male	Total
10—19		1	1
20—29	1		1
30—39			
40—49	1	3	4
50—59	1	9	10
60—69	1	2	3
70—79		1	1
80—89			
Total	4	16	20

TABLE 2

DURATION OF MENIÈRE'S DISEASE FROM THE ONSET OF THE FIRST SYMPTOM TO THE DAY OF EXAMINATION

Duration (years)	Number of patients
< ¼	0
¼— ½	1
½— 1	1
1— 2	1
2— 3	3
3— 5	1
5— 7	2
7—10	4
>10	7

Results

All the patients had a cochlear type of hearing loss which affected both ears in 10 cases, only the right ear in 5 patients, and the left ear only in the remaining 5 patients. In 6 patients the loss of hearing was found to be localized mainly in

the low frequency range. In 9 cases the hearing loss was evenly distributed over all frequences, and in the 5 others it was greatest in the high frequency ranges.

Variations in hearing were noticed in 18 patients and verified by pure tone audiometry in 11 of these patients.

A diminished or absent caloric response was found in 6 cases.

The results of pneumoencephalography are shown in table 3.

TABLE 3

RESULTS OF THE ENCEPHALOGRAPHICAL EXAMINATION

Cerebral atrophy	marked	9 patients
	moderate	5
	slight	3
No certain atrophy		3

The neurological investigation was carried out as described by Monrad-Krohn (1964) Pathological findings were discovered in 17 of the 20 patients investigated, while the neurologic status was normal in 3 cases. In 2 of these latter 3 cases the pneumoencephalogram was also normal. The neurological findings are shown in table 4

TABLE 4

RESULTS OF THE NEUROLOGICAL EXAMINATION

	patients
Disturbance of reflexes, indicating lesions in the central nervous system	13
Romberg' sign present	12
Unstable balance gait	10
Involvement of the cranial nerves (with exeption of the eighth nerve)	10
Paresis, retardation, tonus-changes	7
Disturbance of co-ordination	6
Disturbance of deep sensation	6

Psychological investigation was carried out in 16 of the 20 patients. Signs of organic changes in the central nervous system were found in all those investigated (marked functional disturbance in 6 patients, moderate functional disturbance in 8 patients and milder degrees of functional disturbance in 2 patients)

Other findings were clinical signs of cardiovascular disease in 4 patients a pathologic electroencephalogram in 2 patients, and reduced fields of vision in 2 patients.

Discussion and conclusion

Of 20 randomly selected patients with a classical picture of Menière s disease, 17 had pneumoencephalographic findings indicative of cerebral atrophy a surprisingly high incidence.

In addition to the labyrinthine symptoms, 16 of the 17 patients mentioned had various neurological symptoms. These were, however all moderate. Psychological investigations revealed findings indicative of organic changes in the central nervous system. These observations indicate that the tissue damage and functional changes

giving rise to Menière's disease are not limited to the labyrinth only but in many cases may also include organic changes in the central nervous system

We are not at present able to express any definite opinion on the significance of our findings in relation to the manifestations and pathogenesis of the disease.

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RESULTS OF 10 YEARS STAPES SURGERY

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In the ten year period 1955—65 a total of 751 stapes operations for otosclerosis were performed at the University Ear Clinic, Copenhagen. Of these 373 were direct mobilizations a.m. Fowler and 301 stapedectomies with the Schuknecht technique. A review is given of the results.

At the University Ear Clinic in Copenhagen the first stapes operation for otosclerosis was performed in 1955.

After 10 years activity in this field a follow-up study seems warranted. In the period 1955—65 we operated a total of 751 ears. The main types of operation were direct mobilization and stapedectomy a.m. Schuknecht with 373 and 301 in the respective groups. In the following we shall give detailed results for these two types of operation.

METHOD OF EVALUATION

Results from operations for otosclerosis are often given as percentage of air-bone gap closures, the point of reference being the preoperative bc hearing level. From an immediate point of view it might seem more appropiate to refer to actual bc levels at each follow-up, but then eventual sensori-neural deteriorations caused by the operation were not accounted for. For many reasons the preoperative bc level is not very well defined in patients with bilateral otosclerosis. This is especially true for the poorer ear, which in most instances is selected for operation. Frequently it is impossible to apply adequate masking to the nontest ear. The calibration of bc transducers is precarious and there is no international standard. The use of masking noise will always be necessary in such bc determinations and because of the so-called central masking effect bc levels will appear worse than they actually are by about 8 dB. Furthermore bc levels are known often to change following operations. For these reasons it is possible to register a closure of the air-bone gap even if actual measurement still show some conductive loss, and quite often there will be a so-called overclosure.

In the present investigations we therefore decided to use the average hearing level for air conducted sounds in the speech frequency area (0.5, 1, 2 kc) as a criterion. These values are well defined and the results are rather consistent at repeat examinations. Most patients with otosclerosis have some degree of sensori-neural loss, which sets a limit to what can be obtained by operation, and quite often we will record some persisting hearing loss even if the operative result is optimal. Thus from a statistical viewpoint the results appear less striking than with air-bone gap calculations, but according to our opinion it is an advantage to obtain

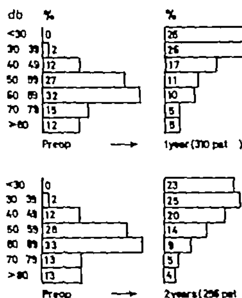


Fig. 1 Results from direct mobilization a.m Fowler Hearing levels have been graded in 7 groups and the distribution between these groups is given in percentages, which are indicated both by figures and by columns.

Preoperative hearing levels are recorded for patients in each individual control group

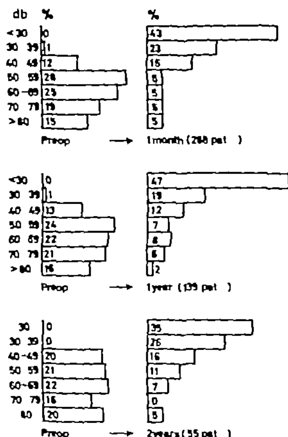


Fig 2. Results from l pedectom m Schuknecht Th method of grouping and recording as in fig 1

a true picture of the hearing level. Experience has shown that this method of control permits a satisfactory comparison between results from various operative procedures.

For practical reasons the hearing levels were graded in seven groups as seen in the graphs. We attempted to obtain systematic controls after one month, three months, six months, one year two years, and four years. If necessary the patients were given reminders by telephone or letters. In spite of this the frequency of control examinations decreased markedly with increased time after the operation. It is our impression, that patients with less satisfactory results are most eager to follow the control schedule.

The graphs give results for one and two years postoperatively For the Schuknecht series we included the results after one month, because of the short period of observation for many patients in this group. Refixation is infrequent with this type of operation and even after one month it is possible to get a fair estimate of the final result.

RESULTS

373 patients were operated with direct mobilization procedures, in most instances according to the Fowler method. The results are seen in fig 1 310 were controlled after one year Only 2 had a preoperative hearing level better than 40 dB and none better than 30 dB At the control 52 % were better than 40 dB and 26% were better than 30 dB Similar results were found in 258 patients that were controlled after the lapse of two years. 110 patients were seen after 4 years. 51% had thresholds better than 40 dB and 30% better than 30 dB

In 13 patients the operation was followed by deterioration of the hearing by more than 5 dB 8 of these had a loss of 10 dB or more. In some the deterioration occurred 2—3 years after the operation and the most likely explanation appeared to be a combination of refixation and spontaneous progression of the disease In two of the patients (0.5 %) there was total loss of hearing on the operated ear

One of these presented an anacusis immediately after th operation. This was uneventful except for very considerabl flow of perilymphatic fluid. It is generally greed that such gushers carry special risk for inner-ear damage following stapes surgery The cause of this is unknown. The ther patient had preoperative hearing level of 63 dB. The operation was difficult, but otherwise uneventf l. One week after the operation the hearing level was 70 dB and after one month 90 dB. At the on and tw year controls there was anacusis. Such tardive lesions have been reported also in other series and again the cause is unknown.

The Schuknecht technique was employed in 301 operations. The results are seen in fig 2. Two years postoperatively 61 had thresholds better than 40 dB and 35 % better than 30 dB By comparison with the one year results there appears to be some deterioration of the hearing levels. Perusal of individual results shows that this is not true, and the explanation should be sought in special circumstances with the group of patients that has obtained the longest observation period. It includes the first patients operated with this technique and undoubtedly there was some selection of the patient material in the beginning so that primarily those

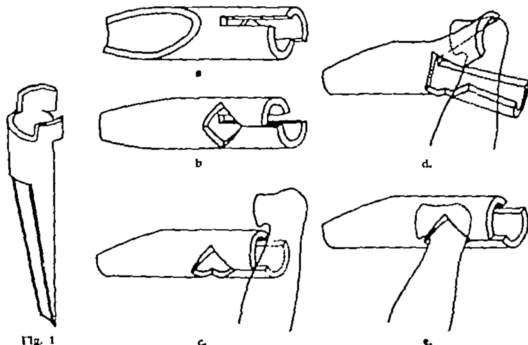


Fig. 2. Prosthesis and its mounting.

We chose polyethylene because it is cheap and easily available, it can be cut to suitable length and shape, and — as already stated — it causes no untoward tissue reactions.

Certain changes in shape have been necessary in order to meet the requirements placed upon such a prosthesis.

At the outset it appeared that these prostheses should have provision for securing them firmly to the long process of the incus. The »wing-grip» model (Fig 1) did much to ensure good fixation. But it was not until the introduction of the latest model, the »*self-locking stapedectomy prosthesis*» (Fig 2) that the requirements seemed to be completely fulfilled

In the wing-grip model, the prosthesis was secured to the long process by means of two wings, each clutching this process, as it were in a grip In my experience the grip has failed in no single case but the new model was devised to give added assurance.

The self-locking model also has two wings which close around the processus longus though in a different manner As long as the lenticular process is in place, it is in practice impossible for the prosthesis to be dislodged To ensure nutrition of the long process, use is made as far as possible of the chorda which is placed over the long process close to the prosthesis, or of a piece of fascia which serves as mediator of circulation from the meatal skin to the long process.

This self-locking prosthesis is relatively easily placed in position. It is pulled over the processus lenticularis like a glove finger The wings then automatically grip the handle of the long process and the lower end of the prosthesis can be inserted at the middle of the window and placed on the tissue used for closure of the surgically created window In cases in which the footplate is thick and the

opening in the plate small, the polyethylene prosthesis can be made very pointed to enable it to fit into this opening The length of the prosthesis can be adjusted in accordance with the distance from the long process to the opening in the window or in the plate, so that there is no danger of the prosthesis sinking too deep in Nor can it do so later since it is held securely in position.

The opening in the prosthesis through which the long process is to pass should be so fashioned as to accord in size roughly with the thickness of the long process. The prosthesis acquires a certain adaptation through the fact that the wings are elastic, i.e. they adjust their position according to the thickness of the processus longus.

In the cases with subsequent inner ear damage, *viz* impaired hearing and giddiness, the prosthesis — in these cases simply a piece of polyethylene tube — sank so deep that the membraneous labyrinth was clearly damaged. This resulted in *one deaf ear Another ear became deaf as a result of an otitis supervening* one month after operation.

Giddiness occurred in the cases concerned, during the first few postoperative days in particular In occasional cases giddiness continued and was observed also later A total of 5 patients complained of more prolonged vertigo In the three most *difficult ones the prosthesis was removed*

The polyethylene prostheses, however have proved very satisfactory in the majority of cases. As late as after 5 or 6 years they functioned perfectly and the patients enjoyed excellent hearing

Table 1 shows the improvement or deterioration of hearing in the cases operated *on* — as indicated by the latest audiograms, made in the oldest cases 6 years

TABLE 1

CO DUCTION (500—2 000 D) CCORDIN LAST UDIO RAMS

Average			
improvement	—40 dB	37 cases	
	30—39	43	
	20—29	40	87.8 %
	10—19	29	
	— 9	16	
Impairment		23	12.2
		188 cases	

TABLE 2

R-BONE GAP CCORD NG TO AST UDIOGRAMS

—10 dB	84 cases	44.6 %	ca. 5 %
11—20	56	29 7 %	
21—30	20		
31—40	14		
41—50	6		
51—	8		
	188 cases		

postoperatively In Table 2 is seen the air bone gap similarly on the basis of the most recent angiograms

In sum it may be stated that a polyethylene tube designed so as not to loosen and to cause no nutritional disturbances in the long process of the incus is reliable and well tolerated. At stapes operations good hearing results have been obtained by using such a prosthesis.

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ANALYSIS OF OPERATIONS FOR OTOSCLEROSIS DURING A PERIOD OF THREE YEARS

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A material of 176 patients operated from the 1st of January 1963 to the 31st of December 1965 is reported. 25 % are examined two years after the operation, more than 60 % are examined one year after the operation and 80 % are examined 6 months after the operation. The patients are mainly operated with the method of the Penn-operation or the stapedectomi according to Schuknecht. A few cases are operated according to Shea or other variations. The two years results in the overall material shows good hearing in 80 %.

It is rather embarrassing to present the results of 176 operations performed during a period of three years, when one reads in the literature of materials consisting of 5—6,000 operations, where follow-up examinations were made, data processing was applied, and, moreover extremely fine results were obtained. The reason why despite this, I am giving an account of some of my results is, that the material reported on has been very thoroughly examined. All the cases, with the exception of 12, have been followed up. As the operation period was from 1 January 1963 to 15 December 1965, some of the most recent cases have not been followed up for more than half a year

Furthermore the material was uniformly investigated from the outset, and, for the most part, the operations were performed by the same operating surgeon, except for a few at the beginning of the period. The operations were mainly performed according to two methods, namely stapediolysis according to Fowler-Holmgren, and stapedectomy according to Schuknecht. The latter method was applied in those cases where stapediolysis failed to give good results. In this connection attempts were made to determine, during the actual operation, whether really satisfactory results had been obtained by means of stapediolysis; and where this was not the case the operating surgeon performed also stapedectomy The cases were followed up by means of control curves 1 week, 3 months, 6 months, 1 year and 2 years after operation.

In this paper the material will not be dealt with in detail, although it would be tempting to do so The purpose of this report is to point out the possibilities of stapediolysis according to Fowler Holmgren. This is a method which, when properly applied to the right case, can give surprisingly good results. However a precondition is, that stapedectomy is immidiately performed unless it is quite certain that adequate results were obtained by the Penn-operation.

Many operating surgeons prefer this simple method, with the retention of as much as possible of the structures of the middle ear to stapedectomy though the latter often gives more certain results. The fact that stapediolysis may necessitate more than one operation has been regarded as one of its disadvantages, since the subsequent operation is much more hazardous for the inner ear If at operation one is strictly critical with oneself however a subsequent operation can be avoided

On investigating the results after two years, when 55 patients were thoroughly examined, it was found that stapediolysis alone had been performed in 28 cases. In 19 of these cases hearing was still extremely good. Moreover in 4 other patients hearing was improved as compared with that at the initial stage. By extremely good results is meant the closure of the air bone gap and by improvement, the closure of the air bone gap to about half the number of decibels. In several of the cases that proved unsuccessful, satisfactory results were obtained by means of a subsequent operation with stapedectomy

The total number of cases, where results were followed up after one year was 70 and in 33 of these cases stapediolysis was performed. In 24 cases there was a total closure of the air-bone gap in six distinct improvement occurred, whereas in tree the conditions remained unchanged. In these three cases another operation has not yet been performed.

Consequently it can be stated that, provided the operation is performed with the absolute precondition in view that total mobilization of the stapes is to be established, excellent results can be obtained. It is not of primary importance to sever the stapedial tendon, but a sufficiently large part of the plate must be retained. The anterior crus and the piece of plate attached to it which together are most often the site affected by otosclerosis, must as a rule, be removed The posterior fragment must be completely mobile in the oval window A piece of gelfoam can be inserted, if anxiety is felt on account of the diastasis which occurs in the window The risk of leakage, however appears to be very slight.

The most usual cause of failure is due to misestimation of the stapediolysis produced inasmuch as the system was assumed to be mobile, whereas in reality it was only a fracture between the anterior crus and the plate. When performing stapediolysis according to Fowler Holmgren, there must be absolute certainty that a mobile connection has been obtained between the remaining fragment of the plate and the incus, belief that this has been produced is not enough Only then can entirely satisfactory results be achieved The test which Lennart Holmgren calls the 1—2 test, and which means that the patient hears better with the tympanic membrane in place, must be absolutely established in order for stapediolysis to suffice without having recourse to stapedectomy Provided these preconditions are fulfilled simple stapediolysis has a position among operative methods for otosclerosis

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RESULTS OF 200 OTOSCLEROSIS OPERATIONS a.m. SHEA

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Since 1959 we at the E.N T Department of the Military Hospital in Copenhagen have been interested in operations to restore hearing including otosclerosis operations. Since its amalgamation in 1963 with the University Hospital (Rigshospital), the Military Ear Clinic has continued work in that field. Use of the Rosen and Fowler operation was soon discontinued because of the many relapses, and this was substituted by Shea s stapedectomy with polyethylene and later teflon prosthesis. This has been used in 200 cases (only one surgeon operating), 182 of which are included in the present material. The remainder have not been observed for a sufficiently long period

The material consists of 60 per cent females and 40 males. It is remarkable that the condition is bilateral in 75 per cent of the females as against only 60 per cent of the males. The majority of those treated were between 30 and 60 years of age.

It has only recently come to my attention that otosclerosis results were to be discussed, so that it has not been possible to compile the material after definite intervals, and therefore the time of the last audiogram taken (2 months to 5 years after the operation) has been employed.

The question as to how the results should be compiled is the subject of discussion. We still think that evaluation of the air-bone gap (pre-operative bone conduction and post-operative air conduction) is practicable, even though the post operative bone conduction often rises (at any rate temporarily) The method is also used in many other places. Mention of the post-operative air conduction alone may be confusing A well-known American otosclerosis surgeon has stated that he would be reluctant to operate if the hearing impairment was less than 20 db! One can certainly agree with him. To state the hearing gain in db per air conduction is also dependent on the starting point. It would be preferable to consider the matter from the rehabilitation point of view — can the hearing aid be dispensed with, completely or in certain circumstances; can a weaker amplification be used, or is the result that an apparently deaf person can use a hearing aid. Furthermore, speech audiometry should be included in the assessment.

Our results with the various methods are as follows (average of 500 1000 and 2 000 Hz): —

TABLE 1

AIR-BONE GAP (POST-OPERATIVE)

10 db or less: in 80 % of the cases
15 db or less: in 94 % of the cases

On investigating the results after two years, when 55 patients were thoroughly examined, it was found that stapediolysis alone had been performed in 28 cases. In 19 of these cases hearing was still extremely good. Moreover in 4 other patients hearing was improved as compared with that at the initial stage. By extremely good results is meant the closure of the air-bone gap and by improvement the closure of the air bone gap to about half the number of decibels. In several of the cases that proved unsuccessful, satisfactory results were obtained by means of a subsequent operation with stapedectomy

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technique is said to give a few per cent more successes. Of course, one should always be prepared to alter the technique (piston, wire, etc.) if the anatomic conditions encountered should indicate the necessity In evaluating the results it should also be taken into account the great experience possessed by many foreign surgeons.

When discussing complications, it is reasonable to divide them into those which occurred in connection with the operation and those occurring later Neither labyrinth infections nor dead labyrinths have been found in connection with the operations, nor was facial palsy seen. In about 12 per cent of the cases it was necessary to cut the chorda or it was torn by mistake, though never bilaterally The only patient who complained was a cook in whose case the nerve was only stretched.

The most interesting group is the 6 per cent with unchanged condition or loss. Of these, 3 were deaf both before and after the operation, 3 had unchanged condition after the operation, 5 sustained cochlear injury to varying extents, one of which occurred in connection with the operation (blood clot in the vestibulum which it was attempted ro remove). After having regained normal hearing, one became almost totally deaf after the elapse of six months, (probable in connection with influenza), while another after hearing well for a year sustained a severe cochlear injury following cranial trauma The question accoustic trauma and stapedectomy should be investigated further

A number of re-operations have been necessary especially among the patients with cochlear injury (explorative operation in 6 cases) and also among those with conductive relapse of hearing. In 4 cases the prosthesis had slipped where the incus was normal, and it was necessary to re-operate in 2 cases where the lenticular process was missing at the first operation. In 6 cases necrosis of the lenticular process was found on re-operation. I do not believe that the prosthesis was responsible for this. Perhaps the surgeon was somewhat unfortunate- it is very easy to fracture.

Re-operations were performed on 20 patients, some several times. Once or twice slight adherences were found in the middle ear but otherwise the middle ear was normal and there was no reaction around the prosthesis. In all cases the membrane in the oval window worked satisfactorily and went over unnoticed into the middle ear mucosa.

Conclusion

With the present technique and instruments, stapedectomy is a justifiable operation in patients with otosclerosis. Restraint should be adopted in the case of very young persons if there is severe high tone loss or if a marble-like, obliterating foot-plate is found.

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LABYRINTH IRRITATION AFTER OTOSCLEROSIS OPERATIONS

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From th Oto-Laryngological University Clinic Turku
(Head, prof. Otto H Meurman, M.D)

The appearance of positional nystagmus was examined in 63 patients during the first postoperative week. In six cases nystagmus was found preoperati ely In 3 cases of these it disappeared in 7 days after the operation. In only 5 cases (7,9 %) nystagmus was not postoperatively registered. In all th others it existed in different forms and types. In 76 % of the cases nystagmus decreased during the first 7 days.

Positional nystagmus of Nylén s type II was most frequent. Only in 3 cases nystagmus of Nylén s type III was found. In most cases the type of nystagmus remaind unchanged until its disappearance.

Only 2 patients had cochlear loss in the postoperative hearing, in one f them it confined to 4 000 cps, and in the other the ear became totally deaf. The latter case is reported more accurately because in this case the patient had both Menière's disease and tosclerosis in the operated ear

The results show that the operative technique which was used, above all, the fascia interposition, does not lead to more serious labyrinthine disturbances than other techniques.

The modern techniques of otosclerosis operations, opening of the oval window completely or partly co ering it with a suitable material and reconstruction of the ossicular chain in some way or other give always rise to some kind of risk to the labyrinth. The immediate injury of the membraneous labyrinth can be avoided in most cases by a well-controlled surgical technique. Opening of the labyrinth, however always brings about a reactive disturbance, serous labyrinthitis, well known in the literature. To which extent the strenght of this depends on the operative technique and on the covering material used in the window is a question which the clinical experience and e.g the animal experiments enlighten rather contradictorily The effect of the primary irritation of the vestibular organ, on one hand, and on the hearing organ, on the other hand, still requires further investigations as to the different methods of the operative techniques.

Material

63 operated patients, who all had a clinical otosclerosis form the basis for this study To 15 patients was performed an solds mobilization operation where the stapes became freely movable. In every case the escape of perilymph from the vestibule to the middle ear could be seen. In 48 cases an interposition operation was performed, where the stapedial footplate was removed and the window was covered by a piece of temporal fascia. To 33 of these a polyethylen tube was put between incus and fascia. In 15 cases one or both of the crura of the stapes could be preserved and were placed on the fascia without opening the incudostapedial joint

and without cutting the stapedius tendon. We have wanted to separate the latter operative technique to its own group because it is often much more difficult than the tube technique and causes more manipulation in the window region than the latter This same operative technique has been used in our clinique since 1959 Results from its effects and complications have been earlier reported (Meurman & Palva 1962, Meurman 1963)

Methods

To find out the vestibular disturbances, the positional nystagmus was examined on several days postoperatively usually on the 1st, 2nd, 3rd, and 7th days. The positions were the supine and both lateral positions. The investigations were always performed in a dark room with the eys of the patient closed. Nystagmus was registered by electronystagmography (Madsen Type 80), the time constant of which is 3" Before every investigation the apparatus was calibrated by 10 degrees movements of the eyes The first postoperative hearing test was carried out on the 7th day when both the pure tone and the speech-hearing tests were performed.

Results

Preoperatively it was verified that 6 patients had positional nystagmus, which after operation disappeared in 3 cases during the first 7 days, and increased in its strenght in 3 cases. One of them had nystagmus of Nylen s type I, and all the others Nylén s type II.

Table 1 shows the frequency and the general nature of the positional nystagmus in all the cases during the first week according to the different operative groups.

TABLE 1

POSITIONAL NYSTAGMUS DURING THE FIRST POSTOPERATIVE WEEK

	Interposit. + Tube	Interposit. + Stapes	Mobilization
Non	3	–	2
Decreasing	24	14	10
Finished	20	7	7
Increasing	5	1	2
Sam	1	–	1
Total	53	15	15 = 83

The figures show that in every operative group, in spite of the surgical technique, the positional nystagmus was very frequent and that it in all groups usually decreased or wholly disappeared during the first week.

Table 2 shows the further analysis of the positional nystagmus during the first 3 days concerning the different Nylén s types.

The most frequent type of nystagmus was direction determined (Nylén s type II) In the mobilization group nystagmus was proportionally more direction changing (Nylén s type I) than in the others, but because of the small number of cases

TABLE 2

CLASSIFICATION OF POSITIONAL NYSTAGMUS

	Interposit. + Tube	Interposit. + Stapes	Mobilisation	Total
Nylén I	2	2	5	9
Nylén II	26	12	8	46
Nylén III	2	1	—	3

there is no reason for more accurate statistical comparison. Only 3 patients had nystagmus of Nylén's type III which we will explain later in this article. Among those 46 cases, where nystagmus was direction determined, it was in 29 cases towards the operated ear and in 17 cases towards the unoperated ear The nystagmus directed towards the unoperated ear never changed its direction towards the operated ear during the first week But the nystagmus directed towards the operated ear changed its direction to the unoperated one in 4 cases.

Table 3. shows the interchanging of nystagmus types during the first week.

TABLE 3

INTERCHANGING OF TYPES OF NYSTAGMUS

	Nylén I	Nylén II	Nylén III
Nylén I 9 cases	6	3	0
Nylén II 46	5	41	0
Nylén III 3	1	2	0

The figures indicate that interchanging of nystagmus was rather unusual.

The last table (Table 4) shows the relation between nystagmus and the improvement of hearing

TABLE 4

HEARING ON 7TH POSTOPERATIVE DAY

Nystagmus	Closure of A B gap	Conduct loss	Cochlear loss
None	34	5	0
Decreasing	11	1	2
Increasing	8	0	0
Same	2	0	0

The figures show that also in the two cases, where hearing tests demonstrated clearly a cochlear injury nystagmus decreased during the first week In one of them the hearing loss covered only the area of 4 000 cps, the other was the before mentioned deaf ear In 6 cases the reason for the conductive loss may be the secretion in the middle ear The later hearing tests showed closure of the air-bone gap.

Discussion

The comparison of vestibular and hearing disturbancies in the otosclerosis material pre- and postoperatively offers many interesting aspects. Preoperatively

Flach (1965) proved that 28,8 % of an unoperated material had equilibrial disturbances. Hearing with bone conduction was in these cases, on an average worse than in cases where the function of the vestibular organ was quite normal. Of the 6 patients of our material, in whom the positional nystagmus was demonstrated preoperatively 5 patients had no symptoms of lesions of inner ear in the hearing tests. They all belonged to the most favourable operation group and they also had the best possible operation result. Only in one case the hearing by air and bone conduction decresed evenly towards the high frequencies. In this case, too the operation gave a good result.

In most cases of our material we found postoperatively a positional nystagmus, which, in spite of the surgical technique, usually disappeared in one week Only in about 16 % it lasted longer Our results in this respect agree with those shown by Bergström & Ivstam (1960) with the mobilization material, but disagree with the results of Flach. In his investigations the maximum of vestibular disturbances existed during 5—8 days, and still months after the operation 32.4 % had disturbances.

Like Ivstam (1962) and Flach we found that the most frequent type of nystagmus was directioned determined (Nylén s type II), and directed towards the operated ear It can be considered as a sign of a rather slight labyrinthine disturbance, as well as nystagmus of Nylén s type I. Nylén s type III, on the contrary indicates stronger vestibular irritation. 3 patients of our material had this kind of nystagmus and therefore it is interesting to examine the hearing results of these patients. The first of them had the best possible hearing result without any signs of cochlear loss. The second had postoperatively a clear loss in the frequency of 4 000 cps, and in the third the hearing totally disappeared. The occurrence of nystagmus of Nylén s type III in the two latter cases corresponds well to the hearing results, but not in the first case. The case in which the ear became deaf is so exceptional that a more detailed data will be given.

Case report. Patient was a 34 years old male, whose hearing had gradually decreased during 4 years in both ears, in the left, however obviously more. In the same time some dizziness had occured, until he, about half a year before coming to the hospital, had two attacks of true rotational vertigo After that the dizziness disappeared. In the hospital normal ear drums were found. The hearing loss in the right ear was by air conduction 35 dB and by bone conduction 5 dB in the middle frequencies. The hearing loss in the left ear was respectivly 60 dB and 35 dB The speech audiograms showed a hearing loss in the right ear of 35 dB and in the left of 65 dB The discrimination loss in the left ear was 16.5 %. Positional nystagmus could not be observed, but a clear canal paresis of moderate degree in the left ear instead. The left ear was operated upon. The stapes was firmly fixed, and in the anterior part of the footplate an otosclerotic focus was verified. The usual interposition operation was performed by using the posterior crus of the stapes. After the operation positional nystagmus of Nylén s type III was registered, which decreased clearly in a week, and wholly disappeared in two weeks. Since the operation the ear has been deaf From this we may conclude that the patient had in the same ear both Menière s disease and otosclerosis. Opening of the labyrinth in labyrinthine

hydrops usually leads to total deafness as has been pointed out before (Meurman & Grahne 1956 Meurman 1959)

Conclusions The results show that opening of the oval window causes labyrinthine disturbances, easily registered by nystagmographic methods. The irritation, in most cases, is slight and does not cause permanent changes in the function of the inner ear We conclude that our operative technique, above all the fascia interposition, does not lead to more serious injuries of the labyrinth than other operative methods of otosclerosis. According to one particular case it seems obvious that when Menière s disease and otosclerosis appear in the same ear a hearing improvement is not achieved by an otosclerosis operation.

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DISCUSSION

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At the Otolaryngological University Clinic, Turku, w have until now performed about 750 interposition operations. From these 6 ears have become totally deaf, 3 as results of direct lesion of th membraneous labyrinth and 3 as late complications (one f them after an acute itis media).

In 60—70 per cent of th cases one or both of the crura have been preserved. W always try to void the use of foreign material in the ear With this method the function of the stapedial muscle is also preserved, at least theoretically

In 30—40 per cent usual polyethylene strut without any special incus-grips has been used. If the lenticular process is well developed, this common type of strut fits very well between the fascia and the incus. If necessary it also can be removed much easier than a strut with special grips.

Since 1959 we hav changed our method very little

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The immediate effect of the procedure can be studied by means of a mirror ttached to the operation table. Primarily the device was constructed for tudying the nystagmus and the facial function during ultrasonic irradiation (Johnson and Stahle 1960). The mirror has also been found suitable for studying the eye-movements during stapes surgery Magnifying glasses according t Frenzel facilitat the observations, and also prevent the patient from seeing the procedure



Fig. 1. The operator gets good lew f the patient face in the mirror The view of the eyes is even further improved by the magnifying glasses. The photograph was taken during ultrasonic treatment of the left labyrinth.

The mirror is plane-surface rectangle 20 × 30 cm (Fig. 1). The arm by which it is fastened to the operation table pivots t three places and so is movable in all directions.

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THE OTOSCLEROTIC SYNDROME

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To illustrate the occurrence of ectodermal abnormalities in otosclerosis, a family is discussed where, in a married couple, exploration of the middle ear has disclosed typically otosclerotic changes. Numerous cases of perceptive loss of hearing are found among the woman's siblings, and one of her three children also suffers from this disease. Furthermore, chronic caries have been found in the milk teeth of three of the couple's 13 grandchildren.

Clinical examination of 256 women with otosclerosis who were examined for occurrences of ectodermal and mesodermal abnormalities demonstrated that these abnormalities were very frequent, especially in patients with hypermobility of the little finger

The results of the above-mentioned examinations, when related to information found in the literature and the previously demonstrated microscopic abnormalities in the skin of patients having otosclerosis, indicate that it is probable that the hearing defect in this illness is but a single symptom in the otosclerotic syndrome.

Through clinical studies during the past 50 years, numerous authors have discovered symptoms in other systems of organs which seem to indicate that the defective hearing of an otosclerotic patient is but a single manifestation of a generalized disturbance.

In Table 1 the observed symptoms which accompany hearing defects, especially otosclerosis, are listed in a tabulation of the works wherein the phenomena are discussed for the first time.

TABLE 1

THE OCCURRENCE OF DEFECTS IN ORGANS OTHER THAN THE EARS (OTOSCLEROSIS, NERVE DEAFNESS)

Findings	Year	Author
Heredit. *fractures*	1788	Ekman
Blue sclerae	1839	Ammon
Blue Sclerae + do	1896	Spurway
Nerve deafness + do + do	1912	Adair Dighton
Otosclerosis + d + do + do	1917	van Hoeven & de Kleyn, Bronson
Defective teeth + do + do + do + do	1921	Stroble
Defective nails + do + do + do + d + do	1924	T kahashi
Defective hair + do + do + do + do + do + do	1932	Ta turri
Defective skin + do + do + do + do + do + do + do	1961	Bentzen

Adair Dighton (1912) during the study of four families with blue sclerae, was the first to draw attention to a coincident occurrence of defective hearing Van der Hoeve & de Kleyn (1917) found 11 persons in one family with blue sclerae and hearing defects, all of which were described as otosclerosis, and Bronson (1917) found seven adults, in a family of eight having blue sclerae, who had developed hearing defects in their youth. Otologic examination of three of them showed that two had otosclerosis and one had nerve deafness. Both Bronson and Spurway

draw attention to the frequent occurrence of dislocations and sprains, which occur just as often as fractures, in Bronson's material. Brittle bones are otherwise not a condition for the occurrence of the other symptoms. Thus, there are but few fractures registered in the case of the family described by Takahashi (1924) in the Tanturri's and Bentzen's material.

As indicated in Table 1 symptoms from other systems of organs, such as the mesoderm (bone, sclerae, joints) ectoderm (organ of Corti, hair nails), or from both embryal membranes (teeth, skin), have been displayed by patients with hearing defects, most often otosclerosis.

In order to examine the frequency of the above-named symptoms, as well as the intensity of their manifestation, a systematic examination of patients who have sought treatment for their hearing defects during the past six years at Statens Horecentral Aarhus, has been made.

Mesodermal abnormalities

It has long been known that the blue colouration of sclerae occurs more frequently in patients with otosclerosis than in the normal population, the frequency is stated to be 60 per cent and 40 per cent respectively The skin in the auditory canal is often atrophic (Holmgren) and the eardrum is often thin, bluish, and semitransparent (Cawthorne). Otosclerotic patients, when questioned as to a predisposition for subcutaneous hemorrhage, either spontaneous or resulting from minor trauma, displayed a higher incidence than the control group. (Table 2).

TABLE 2

FREQUENCY OF SUBCUTANEOUS HAEMORRHAGES IN FEMALE PATIENTS WITH OTOSCLEROSIS

	Females	
	normal subjects	otosclerosis
Number	500	300
Subc. haemorrhages in	43 per cent	68 per cent

A predisposition for subcutaneous haemorrhage, like blue sclerae is a frequently found symptom in inheritable disorders of the connective tissue. Both often occur in cases of Marfan's syndrome, Ehlers-Danlos syndrome, and osteogenesis imperfecta. The occurrence of these symptoms in patients with otosclerosis, which is also a hereditary disturbance, therefore indicates the presence of an otosclerotic syndrome where, in addition to the otosclerotic process in the cochlea, one could also expect to find microscopic abnormalities in other organs, such as the skin.

Skin biopsy was therefore made in otosclerotic patients, Bentzen (1961) and Stadil (1961). The microscopic examination showed. Increase and metachromasia of the ground substance, degeneration of the collagenous fibres and degeneration and increased amount of elastic tissue. In microscopic examination of corium in patients with osteogenesis imperfecta, Stadil (1961) recognized the same changes with corium thinner than normal, the corium contains an increased number of

argyrophilic and elastic fibres, the latter fibres showing a variable degree of degeneration

These equal qualitative histologic changes in the corium in patients with otosclerosis and in patients with osteogenesis imperfecta justified the suggestion made by Wullstein, Ogilvie & Hall (1960) that otosclerosis may be regarded as merely a local form of osteogenesis. A suggestion which these authors had based on the histologic examination of the osseous tissue from the middle ear The osseous tissue has been examined with histochemical staining methods by Arslan & Ricci (1963) who made the conclusion that otosclerosis is a regional mesenchymopathy in the clinical sense like other regional localized mesenchymopathies.

These analyses of histologic and histochemical appearances of the bony and skin lesions of the two diseases appear to confirm the observation by Simson Hall and Ogilvie (1953) that otosclerosis arises from a diffuse alteration of the mesenchym.

The second question, do ectodermal abnormalities take part in the otosclerotic syndrome? will be discussed in the following

Ectodermal abnormalities

The Corti's organ and the dental organ will be discussed in relation to abnormalities among members of a family with marriage between two persons with otosclerosis.

Histologic abnormalities of the inner ear in cases of otosclerosis was discussed by Rüedi (1961) at the 7th International Oto-Rhino-Laryngologic Congress in Paris. He concluded, »The majority of clinicians consider the perceptive element of the deafness which occurs in 30—40 per cent of all cases of otosclerosis also to be due to this disease» The question of »labyrinthine atrophy» resulting from otosclerosis is investigated histologically and clinically by Rüedi in nine cases. New bony formations as well as degenerative changes were observed, and Rüedi considers both changes to be the result of the otosclerotic process.

Histological abnormalities of the dental organ in patients with osteogenesis imperfecta was first described by Bauer (1920) supporting his view that this disease is a »hypoplasia mesenchymalis».

The study of the family (fig 1) is performed to illuminate the question of dental abnormalities in otosclerosis and first of all the question. Is it a possibility that pure perceptive deafness can be a link in the otosclerotic syndrome?

Family with an otosclerotic couple

In 1926 Sinsky presented a family of three *generations arisen from a marriage* between 2 individuals with blue sclerotics, fragility of the bones and deafness Members of the three generations show the three symptoms, blue sclerotics and deafness being most constantly The nature of the deafness is not mentioned

In this family (fig 1 and 2) a man and a woman, both of whom have been operated for otosclerosis, have been married.

Fig. 1 Pedigree of the family of patient (o. 6) married t patient (no. 7) both operated for otosclerosis. All numbered members examined except no. 1 2, 13 and 13 all dead. No. 9 and no. 10 are heterozygotic twins.

The husband (HCÅ 15 410) number 6 in the pedigree (fig 1) His mother (no 1) hard of hearing at 65 years of age, two of her nine sisters were deaf from 40 years of age. A half brother (no. 4) perceptive deafness left ear from 60 years of age, no hearing right ear after radical operation for otitis media and labyrinthitis at the age of 41 years. A sister (no 5) bilateral perceptive deafness from 65 years of age.

Since the age of 25 years increasing bilateral hearing defect. Operation a.m. Shea performed on the right ear at the age of 63 years and on the left ear at the age of 64, with good results.

The wife (HCÅ 1932) number 7 in the pedigree (fig. 1) Her mother (no. 2) bilateral tinnitus from 30 years of age, her father (no. 3) bilateral perceptive deafness from 60 years of age.

Four brothers (no 8, 9 11 and 12) bilateral perceptive deafness from the age of 30 to 40 years, noise trauma possible in two (no 8 and 9) Brother no. 13 died 5 years old, no. 14 stillborn.

Since the age of 20 years increasing hearing defect, first perceived in connection with the first childbirth (no. 15) At 59 years of age very severe bilateral hearing loss (TI 95 db) middle ear operation was performed. ossiculoplastic and fenestratio labyrinthi sin. No improvement from the operation.

The couple (no. 6 and 7) have three children, two sons and one daughter who together with their children are shown in the pedigree (fig. 2)

Son 45 years (no 15) has bilateral perceptive deafness as an isolated C_5 dip = 60 db., possibly caused by 5—6 months of hunting at the age of 17 years. Since then always afraid of shots. Often otalgia during the childhood. His son (no 18) 16 years, has a conductive hearing loss on the right ear possibly catarrh.otitis media.

argyrophilic and elastic fibres, the latter fibres showing a variable degree of degeneration

These equal qualitative histologic changes in the corium in patients with otosclerosis and in patients with osteogenesis imperfecta justified the suggestion made by Wullstein, Ogilvie & Hall (1960) that otosclerosis may be regarded as merely a local form of osteogenesis. A suggestion which these authors had based on the histologic examination of the osseous tissue from the middle ear The osseous tissue has been examined with histochemical staining methods by Arslan & Ricci (1963) who made the conclusion that otosclerosis is a regional mesenchymopathy in the clinical sense like other regional localized mesenchymopathies.

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In this family (fig 1 and 2) a man and a woman, both of whom have been operated for otosclerosis, have been married

years and in her daughter (no. 16) where the audiogram after bilateral stapes mobilisation shows dip = 50 db. at 2000 cps.

In the family of the male probant (no. 6) two sisters of his mother are told to be deaf from the age of 40 years of age otosclerosis combined with affection of the Corti's organ?

Dental abnormalities

As seen from the fig 2, the two married otosclerotic patients have by their three children been given 13 grandchildren, who in each of the sibling groups in 3 children (no 19 20 and 21) had suffered from bad milk teeth. At the time of the examination these have been replaced in two cases (no 19 and 20), while they are still intact in the youngest child (no 21)



Fig. 3. Girl, 6 years old (no. 21) with chronic caries in the milk teeth.

Girl, 6 years, (E T) (No 21).

Odontologic examination shows chronic caries in the milk teeth. Radiographic examination. Panoramix showed no deficiencies in the development of the permanent teeth, or in the tissue producing them. Comprehensive development of caries in the milk teeth, no perforation to the pulpa (E. Mork)

According to the description of the milk teeth in the other two children, one must assume that they also suffered from chronic caries. This disease is characterized by a hard and black affection of the enamel and dentin without tendency to perforation to the pulpa.

It seem significant that the otosclerotic couple have had three grandchildren with chronic caries, among the 13 grandchildren. For this reason one may assume that this condition can be due to an inheritable defect from their father or mother who can have inherited a double factor from their parents in turn.

The observed occurrence of a binaural perceptive deafness in a son subjected to short-term noise trauma, indicates that he, who can have inherited the otosclerotic gene from both parents, seems to have Corti's organs, which are very sensitive to noise trauma.

Three cases of chronic caries in grandchildren and the observed occurrence of binaural perceptive deafness in a son, subjected to short term noise trauma, of an otosclerotic couple indicates the possibility of abnormalities in organs derived from the ectoderm in patients with otosclerosis.

The manifestation of the otosclerotic syndrome in 256 female patients

The preceeding discussion of symptoms in organs derived from the mesoderm and ectoderm of patients suffering from otosclerosis seems to confirm the correct ness of the hypothesis that otosclerosis is a generalized disease. In addition to blue coloured sclerae and a predisposition for subcutaneous bleeding in a sample of 256 women, abnormalities in the nails (soft or flint hard), cranial hair (silky soft or bristly) and teeth have been registered. These patients were asked to state the condition of their teeth in relation to those of their siblings, better or worse.

Coincident with the examination for the above-mentioned symptoms, all of the subjects were given an examination of the flexion of the right hand little finger according to Ellis & Bundick (1956), who used this measurement to determine joint mobility and tissue elasticity Loose-jointedness occurs in the Marfan's syndrome, Ehlers-Danlos syndrome, and in osteogenesis imperfecta. As shown in Table 1 this was first noticed by Bronson (1917) as sprains in patients with otosclerosis.

The measurement is performed as follows The subject places the extended right hand on a flat surface, with the forearm parallel to the surface. The examiner then lifts the little finger as far as is comfortably possible, while measuring the angle between the surface and the proximal phalanx to the closest multiple of 15 degrees. A protractor is not used the angle is estimated

In Table 3 the symptoms under discussion are tabulated in relation to the little finger angle in the cases of the 256 women with otosclerosis, where flexion through an angle greater than 75 degrees is considered to be hypermobility

Total material of females with otosclerosis.

TABLE 3

ECTODERMAL AND MESODERMAL ANOMALIES IN 256 FEMALE PATIENTS WITH OTOSCLEROSIS

	All		Divided according to little finger mobility			
		per cent	≤60	per cent	≥75	per cent
	256		202		51	
Symptoms						
Subc. haemorrhages	154	60	115	57	39	72
Hair	144	56	109	54	3[illegible]	65
Nails	128	50	94	47	31	63
Blue sclerotic	95	37	68	34	27	50
Permanent teeth	95	37	70	35	25	46

As shown in Table 3, all of the symptoms occur most frequently in the loose-jointed patients. In the total sample of 256 patients, there are only 27 persons who do not display any of the symptoms mentioned Among the 202 women

with normal joint mobility (≤60°), 24 persons (i.e. 12 per cent) lacked these symptoms, while among the 56 women with hypermobility (≤75°) there were only three (i.e. 6 per cent) who lacked these symptoms.

The symptoms occur individually or more often, combined. In Table 4 the female patient sample is tabulated according to the increase in the number of combined symptoms.

Total material of females with otosclerosis:

TABLE 4

COMBINATIONS OF ECTODERMAL AND MESODERMAL ANOMALIES IN 256 FEMALE PATIENTS WITH OTOSCLEROSIS

	All		Divided according to little finger mobility			
		per cent	≤60°	per cent	≥75	per cent
	256		202		56	
Symptoms						
Subc. haemorrhages	154	60	115	57	39	70
Hair + do	90	35	66	32	24	43
Nails + do + do	61	24	43	21	18	32
Blue sclerae + do + do + do	28	11	18	9	10	18
Teeth + do + do + do + do	16	6	8	4	8	14

The combination of such symptoms as subcutaneous haemorrhages, fine or bristly cranial hair and soft or flint-hard finger nails occur more frequently in combination with loose jointedness, in 36 per cent of such cases, compared with 22 per cent of the normallyjointed women. If one also includes blue sclerae and teeth which are worse or better than those of their siblings, one finds that all five of these symptoms are found combined four times more frequently in loosejointed women, 14 per cent, compared with four per cent of the normally jointed women.

This plurality of ectodermal abnormalities in nails, skin, and teeth in patients with symptoms known to be connected with connective tissue syndromes (blue sclerae, subcutaneous haemorrhages, and loose-jointedness) must be considered to be an indication that the ectodermal abnormalities are not random symptoms, but express a universal deficiency as a link in the otosclerotic syndrome.

Conclusion

On the basis of the previously discussed collateral phenomena in organs derived from the mesoderm and the ectoderm in patients with hearing defects most often diagnosed as otosclerosis, as well as from clinical observations of the frequency of abnormalities stemming from these embryonic membranes, and supplemented with previously described microscopic abnormalities in skin biopsies from patients with otosclerosis, this disease must be considered to be a manifestation of universal hypoplasia of ectoderm and mesoderm.

Examinations of the siblings and, especially the off-spring of two married individuals with operatively treated otosclerosis show that the condition of Corti's organ also forms a link in the syndrome which is otherwise genetically

determined. Taking note of Bekesy's remarks to the effect that the ear is our greatest skin organ, these conditions were to be expected.

For the sake of clinical work, for an understanding of the occurrence of perceptive otosclerosis as well as for the evaluation of the risks involved in an operation on the middle ear and the vulnerability of the labyrinth and Corti's organ special attention to collateral symptoms in organs developed from the ectoderm and endoderm is of significant importance. One is thereby given the opportunity to judge the extent and the type of the otosclerotic syndrome which like all other syndromes of the connective tissues, can be extraordinarily varied in the manner by which it is expressed.

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DISCUSSION

Bertel Grahne, Helsinki Finland.

In any comparision of the results f the different operative methods for otosclerosis the age of the patients must be taken int account, and hence the duration of the otosclerotic process. The results of the operations in teenagers are usually not long lasting as the process is in the soft progressive stage. I think Professo Diamant also has achieved his best results, with the method he described today in older patients, where the process is in the hard inactive stage.

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Dr Grahn was quite right in stating that the patient's age play part in the choice of operative methods. Many surgeons, who operat for otosclerosis, are aware that certain oval windows have active tosclerosis, whereas in other cases the tosclerosis seems to be completely healed In th latter cases standard tapedlolysis appears t be of definite value.

W th regard t the choice of operative method it would naturally be tempting to discuss the advantages and disadvantages of the different methods. But, since all the operative surgeons have obtained such good results with their respective methods, such discussion must be considered unnecessary

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AN ATTEMPT TO MAKE AN AESTHETIC EVALUATION OF OPERATION FOR MANDIBULAR PROGNATHISM

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Most people who have a very obvious mandibular protrusion, consider it to be ugly and depressive and this is good reason in itself for operating, even if an objectiv observer may be hesitant about th new character of the face that correction makes. This is especially the case when the concave profile has been changed into a convex one with a retired chin depending upon the consolidation of the bone fragments in position n t projected. Author has shown about one hundred persons pictures of the profiles before and some years after the operation next to one another on screen and asked them to evalu te the aesthetic result by using a scale of marks that has permitted relatively large graduation.
(To be published in Acta Odont. Scand).

INORGANIC BONE AS FILLING MATERIAL IN BIG MANDIBULAR CYSTS

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From the Central Hospital of Joensuu

The author demonstrates his method of filling big mandibular cysts with inorganic heterogenous bone. In authors opinion this method is superior to the old marsupialisation methods because of rapid ossification of the operative cavity

Enucleation and obliteration have become the established surgical methods in the treatment of big mandibular cysts. This method attempts to restore the original strength and shape of the mandible, which from the orthodontic point of view is essential if the former functioning is to be re-established.

Several obliteration methods have been proposed. Blackstone has employed freeze-dried bank-bone, Macomber used iliac bone chips, and Thoma used Gelfoam. Filling of the cavity has been accomplished by all these methods. The recovery process has been investigated by Jenkins and Clarke. According to their studies the gelatin sponge is absorbed in six weeks, and osteoblasts and new bone are formed out of the periphery in place of it.

An obliteration operation must meet certain general requirements. It is, first of all, of utmost importance that the cyst should be completely removed, as recidivism, in particular of big cysts, is very common. On occasion the malignisation of a recidivated cyst also occurs. The operation must be such as to preserve the original shape of the mandible, for only then is it possible to obtain the optimum orthodontic result. It is also important that the dental prosthesis be made as soon as possible after the operation to prevent atrophy of the mandible and asymmetry

Own Experience

In the course of several years the author has employed heterogeneous inorganic bone in the filling of big mandibular cysts. During the operation particular attention has been devoted to the complete removal of the cyst sac, and to ensure this the inner surface of the bone cavity has also been scraped after the removal of the cyst. Sulfa-penicillin powder was blown into the cavity before the obliteration. »Ossar» — a product of the Finnish Lääke Oy — an inorganic granulate prepared from cattle bone was used as filling material. Ossification of the preparate has been previously established (Härmä & Koskinen) when used in attico-mastoidectomy operations over several years.

6 big mandibular cysts have been operated upon by the method described during the last three years at the Otological department of the Central Hospital of Northern Carelia. A more precise distribution of the material appears in Table 1

TABLE 1

Case	Age and sex	Diagnosis	Size	Control time
1 ER	13 fem	Neurinoma et cysta follic. —5 (fig. 1)	4 ccm	9 months
2 AL	20 male	Cysta radic. inf c. fistula reg. 8—7—6—	12 ccm	10
3 AH	29 male	Cysta mandibul recid. l dx.	75 ccm	4
4 JK	31 male	Cysta mandib inf. l. dx. (Fig. 2.)	28 ccm	16
5. VR	42 male	Cysta radic. —7	2 ccm	8
6. JS	67 male	Cysta mandib l. dx.	51 ccm	3



Fig. 1 Case 1 Before and 9 mo ths after operation.



Fig. 2. Case 4 Before and 16 month fter operati n.

Case 3 (AH) was operated upon for the first time in 1958 and a new cyst formed almost immediately About a year subsequent to the first operation a suppurating fistula had formed buccally



Fig. 3. Case 3. Lamellar bon with connectiv tissue.

In the second operation a 75 ccm infected cyst was removed and »Ossar» was used for the filling There remained a fistula in the operation wound for a period of three months. Two years subsequent a new smaller cyst was found in an X-ray examination in the middle of the site of the previous cyst, and a new obliteration operation revealed a 48 ccm hollow cyst coated with granulate tissue The cyst was re-filled with »Ossar» and three months after the latest operation the ossification appears from the X-ray picture to be good. A fistula of approximately 2 mm diameter was remained in the operation wound for a period of 2 months.

In the other cases also with the exception of cases 1 and 5 there has been a fistula in the operation wound for some length of time after the operation These have closed spontaneously in a few weeks and have left no impairment.

Prosthetic measures were begun a month after the operation in all the cases despite the fact that the fistulae were open. Nor has there later occurred any change in the outward shape of the mandible at the site of the operation and consequently it has not been necessary to renew the dental protheses. The ossification was followed by means of radiography In case 3, in which a recidive cyst arose, a resorption site which later became a cavity formed in a couple of months in the middle of the transplantation bone. In the other cases the granularity of the artificial bone disappeared in the X-rays in the course of a couple of months while the homogenic structure of the bone was preserved. This was interpreted to the effect that the transplant bone is resorbed within two months and new bone is formed in its place within this period In case 3 a sample of the re-formed bone was taken in the last operation and it was found to be mature lamellar bone of the same type as we found in our previous investigation after the filling of the mastoid cavity Further it was found in case 1 that a new tooth is able to cut through the »Ossar» in six months.

Discussion

According to radiological examination the formation of the new bone takes place from the periostium by the ossification first of the periphery of the filled cavity

and only thereafter of the centre. It consequently appears preferable to remove a minimum of bone from the surface areas of the cyst. It has been found that the artificial bone is absorbed down to the level of the surrounding bone, so that no curved bone formation can thereby be built. An extremely thin bone — often paper thin — as frequently exists on the surface of cysts, is however able vigorously to accelerate ossification. This is why I have removed bone from the surface of the cyst only to such an extent that it is certain that the membrane of the cyst has been absolutely removed. After operation hematoma tends to occur at the centre of large cavities. In case 3 this has led to the occurrence of a bone cyst in the middle of the transplanted bone. In my later operations I have employed the method recommended by Thoma to moist the bone granulate in thrombine before filling, whereby no real separate accumulation of blood will occur and there will be coagulate only between the granulae. It is necessary for the same reason to be most careful with regard to hemostasis. I have, however not employed diathermy for bone bleeding but have staunched the bleeding by crushing the end of the bleeding vessel.

In many cases a fistula of the incision developed post-operatively This was apparently due to the fact that during the operation saliva had run into the wound All the fistulae did however close by themselves and they did not apparently have any effect upon the ossification. With the exception of one case neither did transplant bone ooze out through the fistulae. It was possible to use a dental prosthesis without difficulty as early as a few weeks after the operation in spite of the open fistula.

In my opinion the surgical method I employed has the following positive aspects.

1 Ossification begins quickly and takes place completely
2. After ossification the shape of the mandible is retained.
3 After complete removal of the cyst, recidives cannot occur and mesotelial retention cysts occur to a lesser extent than when soft filling material is employed
4 Once ossification has taken place resorption no longer occurs as may be the case when the patient s own bone is employed as transplant.
5 Any infection of the incision will in no way affect the transplant, as this consists entirely of inorganic material.

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DISCUSSION

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The cases described by Koskinen were all located t the mandibulum. When operat g large dental cyst in the upper j w there certainly is no indication for filling of the remaining cavity after extirpation f large medial cyst th cavity should be connected t th bottom of the nasal meatus; the cavity remaining after extirpation of large lateral cyst should be connected t the maxillary sinus.

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Mårtensson In some few cases I have put bone chips in the operative cavity after big cysts of the mandible I didn t find better or more rapid healing than after general operation without bon implantation.

Pindborg In the case of experiments w th implantation of inorganic bone tissue int cyst cavities, control series treated by the Partsch II method must alway be allable W have found, t the Dental Clinic of Rigshospitalet in Copenhagen, that inorganic bone is absorbed ery slowly — When reporting on possible recurrence of cy ts the histological diagnosis should be tated. The picture may be distorted by the presence of dentogenic kerato-cysts seeing that this type of cyst tends to recur in about 60 % of the cases.

STUDIES ON THE INNERVATION OF TASTE BUDS

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The innervation of the taste buds has during the last years been the subject of extensive interest from a structural viewpoint. From a functional point of view too an increased interest of the problem has aroused.

At the great numbers of otosclerotic operations that now is performed the chorda tympani in not few cases is injured and taste disturbances follow

Against this background the author has begun a detailed study of the structure and innervation of the taste region.

There is unanimous agreement that the principal peripheral taste receptors in man and animals of higher order are situated in special cell-groups, taste buds, *on the tongue and in the throat.*

In basic works by Pfaffmann, Zotterman and many others, problems of anatomical and physiological nature about the sense of taste have been thoroughly discussed It is therefore surprising that in such a modern work as de Lorenzo s study (1963) on the ultrastructure of taste buds we can find, »The innervation of the gustatory receptors remains obscure» It is extraordinarily difficult to follow the individual fibres in the rich nerve plexus situated just below the base of the taste buds and de Lorenzo writes, »Identifying synaptic junctions with any degree of reliability becomes extraordinarily difficult and most times impossible».

From a theoretical point of view problems concerning the structure and function of sense organs are always of great interest. From a clinical point of view the structure and innervation of the taste buds is also very interesting and the consequence of injuries to the neural pathways has become of great importance. In modern otosurgery we often work around the chorda tympani, a nerve transmitting a great part of the sensation of taste from the tongue Injuries to the chorda tympani are not uncommon and have aroused considerable interest at many places in the world. The problem has been approached in different ways but in general the damage caused has been studied by electrical test-methods.

Against this background we have found it to be of great interest to attack the problem in a slightly different way First we shall describe the normal structure of the peripheral taste sense receptors. After injuries to the innervation of a sense organ there will be disturbances in the normal function as a result partly by modified conduction properties and partly by changes inside the receptor organ It is known from earlier investigations that injuries to taste nerves will be followed *by degeneration of the taste buds. The examinations are however not quite con*clusive. We have therefore started to transect the taste nerves and have then analysed the morphological changes of degenerative nature in the taste buds.

From the Ear Nose and Throat Department of the University Göteborg (Head: O. Herberts). This study has been supported by grants from U. S. Office of Naval Research (Contract No. N62558 1261 with H. Engström) and by the Swedish Medical Research Council

Special attention has been devoted to the nerve structures. The work is intended as an experimental and clinical study and this report is of preliminary nature.

Material

Temporal bones from adult humans, fixed in 10 formalin, were used for the anatomical studies of the chorda tympani.

For our animal experiments we have used rabbits with a weight of 1,5—2 kg. Test objects have been the papillae foliatae on both sides of the tongue. These papillae have been examined both in normal animals and in animals where the glossopharyngeal nerve has been transected. The operations have been performed in general anaesthesia (Mebumalsodium, 6 %) and with local injection of xylocain-exadrin (0 5 %) to reduce bleeding

The specimens have been fixed and stained by:

(1) Maillet's modified zinc-iodine (NZ) method (Engström, Ades and Andersson, 1966).

(2) 1,5 % veronal-buffered osmiumtetroxid

As embedding we have used epon and acrylate.

Anatomy

The taste buds have developed as special cell groups from the surface epithelium and answer to chemical stimuli. Generally the taste buds are situated in groups on papillae which have different form. Normal function of the taste sense organ needs intact nerve supply

There has been much discussion concerning the pathways for taste from the anterior two-thirds of the tongue. Today the general agreement is that the chorda tympani, one portion of the lingual nerve, conducts taste impulses from this region of the tongue (Cushing 1903, Lewis and Dandy 1930, Schwartz and Weddell 1938, Pfaffmann 1951) From the posterior third of the tongue taste fibres run through the glossopharyngeal nerve while the vagal nerve conducts taste impulses from the pharyngeal and laryngeal regions. In human beeings the chorda tympani after leaving the lingual nerve deep in the infra-temporal fossa passes the medial pterygoid muscle and runs to the base of the skull. The nerve traverses the middle ear and joins the facial nerve proximally of the stylomastoid foramen in the facial canal The fibres then follow the facial nerve to the geniculate ganglion, where they leave the nerve and pass through nervus intermedius of Wrisberg to the nucleus of tractus solitarius (Lussana 1869 Ranson 1935, Zotterman 1935, Pfaffmann 1959 Krarup 1965) To this nucleus the glossopharyngeal nerve and the vagal nerve also transmit taste fibres. The nerve supply is chiefly homolateral.

While the investigations of the peripheral pathways for taste fibres in the main are based on clinical observations in man it has mainly been possible to attain knowledge about the further central course by experiments on animals. The secondary gustatory neurons origin from the nucleus of tractus solitarius and run through the opposite ascending medial lemniscus to the arcuate nucleus of thalamus (Börnstein 1940, Benjamin and Pfaffmann 1955 Andersson and Jewell 1957 Cohen, Landgren, Ström and Zotterman 1957)

The cortical representation of taste is in all probability situated at the post central gyrus (Adler 1935, Börnstein 1940, Benjamin and Pfaffmann 1955, Benjamin and Emmers 1960).

The taste buds are small ovoid formations with a distinct base and top and with curved sides. Within the top a small taste pore can be observed. At the base nerve fibres enter the buds. The region immediately below the taste buds is from a morphological point of view very interesting. In this area a great number of nerve fibres before entering the taste buds lose their myelin sheath and run unmyelinated intragemally (Retzius 1892, Kolmer 1910, Engström and Rytzner 1956, de Lorenzo 1963, Farbman 1965).

Results

I. *Preparation of the chorda tympani*

Every oto-surgeon knows that the chorda tympani may have a varying course inside the middle ear. To get a clear view of the course not only in the middle ear but also in the mastoid bone we have dissected the nerve in nineteen human temporal bones. The tympanic membrane has been elevated and the chorda tympani then becomes visible in the middle ear. In some cases the nerve has in the middle ear an almost vertical course, almost hidden behind the posterior edge of the tympanic sulcus. In other cases chorda tympani has a more horizontal course. It is easily understood that in these cases the nerve can form an obstacle at operations in the middle ear.

After cutting the tendon of the tensor tympani muscle at its attachment to the malleus, this bone can be removed. In man the chorda tympani passes above the insertion of the tensor muscle on the malleus. According to earlier investigations the chorda tympani in Rhesus monkeys courses above this insertion also while in other species as cat, dog, rabbit and ox it passes below the insertion of the muscle (Gray 1953).

By means of a drill the chorda tympani is uncovered to the point where it joins the facial nerve. The distance between the stylomastoid foramen and this point is measured. See table 1.

TABLE 1

DISTANCE FROM THE STYLOMASTOID FORAMEN TO THE ENTRANCE OF CHORDA TYMPANI IN THE FACIAL NERVE

Specimen No	Distance (mm)	Specimen No	Distance (mm)
1	2,5	11	Below stylomast foramen
2	0,3		
3	0,6	12	2,8
4	1,8	13	3,1
5	3,9	14	0,1
6	0,9	15	1,6
7	6,8	16	5,1
8	6,8	17	0,7
9	0,7	18	1,0
10	8,9	19	3,8

From this table it can be seen that the distance may vary considerably In one case the chorda tympani joined the facial nerve below the stylomastoid foramen.

II *Normal structure of taste buds*

For our experiments we have used the foliate papillae on the tongue of rabbits. These papillae are situated in a distinct group on the lateral posterior part of the tongue where they form a distinct area of ridges separated by furrows. Along these furrows large numbers of taste buds are found. (Fig 1).



Fig. 1. Papilla foli tae (FP) from the tongue of rabbit. The taste b ds (TB) situated along the furrows. Not the different staining of different parts of the surface epithelium. N = nerves. NZ-staining. Phase contrast microscopy Magn. 155 ×

Immediately after killing the animal by air embolus the tongue is taken out the foliate region exised and divided into suitable parts, fixed and stained in one of the above mentioned solutions. After dehydration the specimens are embedded in epon or acrylate and sectioned with microtome or by hand.

The zinc-iodine or Nz-stained specimens have been investigated in light or phase contrast microscopes were they show a differential staining of the various cell structures on or inside the papillae. The surface epithelium and the epithelium at the base of the furrows take up the stain in a different way (Fig 1). In the taste buds we find the taste pore with a great number of villi and at the base the entering nerve fibres (Fig 2) Light and dark cells can be distinguished inside the taste buds. Among the latter cells there are two types, one with the nucleus just in an equatorial plane and another with the nuclei at lower third of the taste bud. The light cells are scattered between the darker one It is possible to follow a great number of nerve structures from the taste buds to underlying tissues (Fig 3).

An earlier interpretation was that there in the taste buds were two distinct cell types, namely sensory cells and supporting cells (Heidenhain 1914) Recent investigators, among others Engström and Rytzner (1956), de Lorenzo (1963), Farbman (1965) have suggested that there may be only one type of cells, which in various stage of growth and function have a different appearance



Fig. 2. Taste bud with taste pore and villi (between arrow). At th lower part of the micrograph is the base with entering nerves NZ-staining. Phase contrast microscopy Magn. 1560 ×



Fig. 3. T te bud with very distinctly appearing dark (black arrow) and light (white arrow) cells. NZ-staining. Phase contrast microscopy M gn. 780 ×

The examination has showed that there are different cell types with different staining and structure. If these differences among the cells are signs of differences in cell type or indicate a different physiological condition in one single type of cells can not yet be completely settled. It seems quite probable, however that there are different cell types with various function Of great interest is the observation that the surface epithelium takes the stain in a different way in special regions. This may be an indication of a different enzymatic activity in different regions.

III *The structure of taste buds after nerve section*

As mentioned earlier the organ of taste needs an intact nerve supply for a normal function Experiments have shown that after transection of a gustatory nerve there will be degenerative changes in taste buds belonging to the corresponding region (Olmsted 1920 and 1921 Whiteside 1927 Torrey 1934, Guth 1957). According to Olmsted and Torrey there is a neurohumoral factor This investigators have carried out their experiments in the cat-fish and found that for several days after a nerve section there will be morphologically intact taste buds, which then abruptly degenerate and disappear in a few days. This neurohumoral substance that is found in the distal end of the severed nerve has then been consumed. A longer distal nerve-stump should then give a longer survival time before degeneration starts. If the cut ends are sutured giving a nerve-continuity this is followed by reappearance of taste buds (Olmsted 1920 Whiteside 1926, Guth 1958).

Experiments on rats by Guth (1957) have however shown that the mechanism with a humoral substance at the degeneration did not exist. The degeneration in the taste buds is starting as early as one day after nerve section After seven days they could not identify taste buds and the epithelium is beginning atrophy

We have transected the glossopharyngeal nerve in fourteen rabbits. The nerve is sectioned about 5 mm distally to the jugular foramen by a incision just below and behind the mandibular angle. A week later the rabbit is killed and the foliate papillae prepared in the same way as is described under II

The examination of the »Nz-stained» specimens with light or phase contrast microscope shows as in the normal cases a different staining both of the surface and of the underlying structures. No structures corresponding to normal taste buds can be observed. There exist only some intensely staining cell-like formations which without doubt are results of the degenerative process in the taste buds and the epithelium (Fig 4)



Fig. 4. Section through furrow between two foliat papillae as seen one week after unilateral sectioning of the glossopharyngeal nerv Different phases of degenerating tast buds (TB). Normal tast buds are not seen in this region. NZ-staining. Phase contrast microscopy Magn. 780 x

Our experiments have shown pronounced cellular destruction after transection of the glossopharyngeal nerve. They have been done partly to develop an appropriate method for fixing and staining of these specimens and partly to develop a good technic of preparation. The results have shown that it is possible by using the described methods to follow the different stages in the degeneration of taste buds. By combining the present technic with electron microscopic examination, for which purpose the same fixation and embedding can be used, we hope to be able to elucidate in detail the process of degeneration and regeneration inside the tongue and especially in the taste buds. Further studies with different survival times of the animals after nerve section are now progressing

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DISCUSSION

Wiberg, A.: It was interesting to hear dr Jeppsson observations how varying the chorda tympani leaves the facial nerve. As far as I know this material is the largest concerning this question. The authors findings would mean, that one should be careful t draw too great conclusions about taste disturbance or not in the level diagnosis of facial palsy.

I have since three years been occupied with a follow up examination concerning taste and salivary secretion in cases of chorda tympani damage or section in operated otosclerosis patients.

On the tongue one can see remaining papillae on the operated side especially on the tip and gradual decrease of papillae against the dorsum of th tongue. With electrogustometry and taste solutions I have found a gradually decreasing taste threshold against the tip of the tongue on the operated side. This would mean a certain degree of cross-innervation of the tast papillae especially at the tip of the tongue.

Remaining papillae and cross-innervation in the mid-line was anatomically described by Zander in 189?. Several authors, a.o. Dastur have found richness of taste fibers apically where ma y fibers end interpapillary that is to say that the tast papillae might not alone subserve the taste function.

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P. H. J ppsson to dr. Wiberg

Yet we have on'y examined taste buds from the papilla foliatae region of the tongue. Now when w have a good technic f r preparation, staining and fixation w are planning to examine t st bud from different region of t ngu of m n both during normal condition and after injuries t the taste nerves.

STYLALGIA

CLINICAL EXPERIENCES OF 52 CASES

Risto Härmä

Kuopio, Finland

From the Central Hospital of Kuopio

Stylalgia occurring in connection with the elongated tyloid process is more common than is generally thought. Most f the 52 cases were diagnosed over period of 2 years in hospital area consisting f 300,000 inhabitants. The youngest patient was 29 and the oldest 83 years old t the onset of symptoms. The ratio of men t women was 2:3. The characteristic symptom is pain below the angle of th mandible nd mostly also in the throat. Often pain radiates to the ear and sometime s t the cheek, jaw eye or lower neck. Turning of the head may increase pain. Diagnosis rests on characteristic symptoms and palpation of the tonsillar region but it should be confirmed radiologically if the tender styloid tip is not clearly felt. Bilateral elongation occurred in about fifty per cent of cases, but only half of those had bilateral symptoms. 46 patients were operated without complications and the majority experienced relief from their symptoms. Stylagia develops either in connection with the calcification of the tyloid process t the age of 29 t 41 or later as result f throat infections, traumas, ageing phenomena of cervical spine etc.

Stylalgia is a pain syndrome occurring in connection with an elongated or malpositioned styloid process. Most authors believe it to be more common than is generally supposed, and in my opinion it is one of the most common pain syndromes of the regions of the head and neck.

Most of the studies published on stylalgia have been small ones, the majority being based on a few cases only There have however been some larger studies, the following of which may be mentioned Fritz s 43 cases (1940 America) of which 11 were operated on, Eagle s 254 cases (1948, America) of which only 44 were operated on, 1962 Eagle had over 100 cases operated, Lajda s 61 cases (1958, Czechoslo akia), and Nara s 32 cases (1958, Japan). The complex of symptoms has been known since the last century although the cases published earlier were either quite exceptionally elongated styloid processes projecting into the throat, or cases in which the whole styloid system had ossified (v Eichen 1919 Bernfeld 1932)

Eagle (1948 1949) has published a study of the carotid artery syndrome caused by the styloid process, in which the pain spreads chiefly to the neck, face and eye. Laskiewicz (1953) and Ascherson (1957) have shown that the styloid process may cause a state of pain resembling glossopharyngeal neuralgia. Lajda has emphasized the diversity of the symptoms in the region of several cerebral nerves.

Eagle claims that the headaches and other pains of numerous patients are often treated under faulty diagnosis which does not connect the pains with the styloid process. This is probably true, at least in Finland (Aro 1965) To obtain a better picture of the diverse symptoms of the styloid process syndrome, we have paid

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special attention in our hospital to the styloid process in all pain states of the region of the head and neck The styloid process has been palpated irrespective of whether there are pains in the throat and an X ray examination has been made in all unclear cases. Spurred on by some encouraging cases we have suggested surgical treatment to the patients concerned in those cases in which there has been reason to suspect that an elongated styloid process has contributed to the pain.

In our hospital circuit of 300 000 inhabitants, material comprising 52 patients has accumulated in 4 years. 46 were operated on and 6 were not. The material is relatively recent, as 37 cases were diagnosed last year up to May Two thirds of the patients came under treatment during the cold season between November and April.

There were 32 women and 21 men

The youngest patient was twenty-nine and the oldest was eighty three upon arrival for treatment The duration of the symptoms before treatment varied between some few months and over 20 years. The age at which the symptoms appeared is shown in figure 1 It can be seen that the symptoms first appeared in about half the patients when these patients were in their thirties, whereas the rest of the cases are distributed fairly evenly among the older age groups.

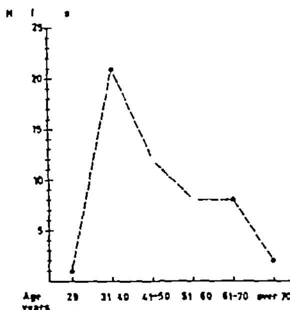


Fig. 1 The ages of the 52 stylalgia patients.

The records of the out-patient department show a frequency of stylalgia patients of approximately 1:250 and of patients admitted the frequency is 1 10. The prevalance of stylalgia also appears from the fact that the number of these patients has been about half the number of the tonsillectomy cases over thirty years of age It must however be noted that we have paid special attention to this particular syndrome but although the collection of material has been terminated it appears that the number of cases is still increasing rapidly

The following presents as symptoms of stylalgia only those symptoms which appeared in patients operated upon and which were entirely removed or considerably relieved These symptoms and their frequency appear in the following table.

Pain in the neck	22
Pai in the throat	19
Pai in the ear	21
Sense f lump in throat	7
Pai in swallowing	7
Pain arising from change i the position of the head	7
Headache	7
Eye-ach	6
Cheek-ache	5
Tongue-ache	5
Sensation in the throat f increased saliv secretion	5
Pai i gums	3
Pain in the shoulder	1
Pai i the nape f the neck	1
Pain in the jaw	1
Hoarseness	1

I should particularly like to stress the fact that the chief symptom is a pain or a slight ache in the neck below the angle of the mandible while pain or pricking sensation in the throat takes only second place. In addition to the above, in most cases pain radiated to the ear but this did not occur in all cases. On the other hand painful swallowing, contrary to what might be thought, is not a common symptom. Most frequently the pain occurs regardless of swallowing although swallowing may cause intensification of pain. The material did not reveal any distinct groups. All the patients complained of something in the neck or throat It was aching, stinging or shooting pains, and in some cases only the sensation of a foreign body

In 10 instances, however the pain also radiated to the eye, to the cheek beneath the eye, or to one side of the head. 8 of these had earache as well as a throat sensation.

In 4 patients the primary pain was felt in the gums, in the palate or in the tongue in addition to the throat sensations.

Chronic tonsillitis is a conspicuous complication in the material as a whole. Tonsillectomy or tonsillotomy had been performed on 10 patients prior to their arri al for treatment. It had been recently performed upon 5 of them in the belief that the stylalgia had been caused by chronic tonsillitis. Styloid resection was successfully performed upon all of these. In addition to the above, chronic tonsillitis could be diagnosed in another 20 cases.

Only eight of the successfully treated patients revealed no symptoms of tonsillitis. One of them had a completely ossified styloid system on one side, with a pseudarthrosis in which an arthrosis deformans had developed (Fig. 2)

X-ray revealed deformities in the spine at the neck in 7 successfully treated patients, but only 4 had rheumatic symptoms.

The pre-operative diagnosis was based on the typical symptoms and in most instances on the sore point of the styloid process, which could be felt with the fin-



Fig. 2. 67 year-old male patient. Styloid proces ossified on the right sid t the hyoid bone with pseudarthrosis.



Fig. 3. Elongated styloid processes, l sid iew

ger at the front or lateral side of the tonsilla The adherent tonsil or the post operati e scars often prevents the point from being felt and it is likewise impossil le to feel a styloid process that has ossified all the way to the hyoid bone but the oreness is evident also in these cases. There is often soreness under the angle of the mandible also It is easy to confirm doubtful cases by radiograph If the styloid processes in a side view project downwards much beyond the first

cervical vertebra and approach the angle of the mandible, they must be regarded as being elongated (Fig 3)

In differential diagnosis special attention must be paid to a chronic tonsillitis. A large part of the patients above thirty years of age whose throat pains are not cured by tonsillectomy are stylalgia patients. We were once mistaken ourselves because of a hypopharynx carcinoma in its initial stage which was not revealed in the first X-ray examination.

Special attention should also be paid to the various types of pharyngitis, migraine, ganglion pterygopalatium-neuralgia, the diseases of the temporomandibular joint and faults of dental prostheses. Tumors of the pharynx or the base of the tongue rarely cause difficulty in differential diagnosis.

27 out of the 52 patients had a styloid process elongated on the one side only with one-sided symptoms. 25 patients had a styloid process elongated on both sides, but only ten of them had symptoms on both sides.

18 patients of the 40 successfully treated had as styloid process elongated on both sides, but in 10 of these cases one of the styloid processes was without symptoms.

The treatment was exclusively a resection performed through the mouth. It was mostly performed after tonsillectomy when the operation is very easy The point of the styloid process, which can be felt through the tonsil cavity was prepared bluntly bare by using a long Killian speculum as a spreader The periostium is cut at the point with a scalpel and the ligamentum stylohyoideum is sharply severed. The preparation is continued upwards as much as can easily be done, and the styloid process is cut with sharp pincers. The incision is closed with cat gut stitches.

The length of the removed part of the styloid process varied from 7 to 22 mm half of the styloid processes removed measuring 11 to 15 mm.

A simple styloid resection without tonsillectomy was performed under Carbocain® anasthesia on two patients with organic heart trouble. The incision was made in front of the tonsil of the fore palatal arch, and the method was the same as above If the tonsils have been removed previously the incision should be made at the site of the point of the styloid process and the wound should be spread bluntly to prevent bleeding

A resection was performed from the throat side on a patient whose whole styloid process system had ossified to the hyoid bone. It seems, however that in cases like this an external operation is simpler

In clear one-sided cases the resection of the styloid process was performed only on the one side. In 3 of these cases, however the symptoms have recurred on the side not operated upon. If removal of the tonsils was necessary because of chronic tonsillities the removal of a symptomless styloid process, if elongated, was usually attempted.

40 patients became free from symptoms, 4 showed improvement, and in 2 cases the treatment did not affect the symptoms. One of the two last-mentioned cases was a dystonic. 6 were not operated upon because their symptoms were mild ones, because of the unwillingness of the patient, or because of complications increasing the risk.

No complication or bleeding worth mentioning occurred in connection with the measures taken.

The etiology of the styloid syndrome has not yet been fully explained. The cause is generally held to be compression of the glossopharyngal nerve or of the wall of the pharynx, or of carotid artery brought about by an elongated or malpositioned styloid process. Apparently other nerves too such as the chorda tympani and the lower branch of the trigeminus, may suffer compression

The largest group in my material, i.e. those aged 31—40 appear to be cases in which the styloid process, when ossifying, immediately forms in such a manner as to cause compression symptoms.

There must, however be other factors present. It can be concluded from the two-sided cases that at least every second styloid process is free of symptoms and that there must be twice as many elongated styloid processes completely free of symptoms as there are elongated styloid processes causing symptoms. Why then, does an elongated styloid process previously free of symptoms start in some stage of life to cause symptoms? This stage occurred in the oldest patient only at the age of 83

Some investigators, such as Layani, see the cause in rheumatic styloiditis caused by pharyngeal infections. On the basis of my own material, too infections have an evident effect on the onset of symptoms, but although a histopathological examination of 5 styloid processes and the attached stylohyoid ligament was made no changes due to inflammation were observed.

Trauma is a possible cause of the onset of the pains. Hilding (1961) et al. have published fracture cases that caused pain. On the other hand, fracturation by the finger has previously been used as treatment In one of my own previous cases palpation by finger caused fracture but the patient's symptoms ended there with.

A tonsillectomy may be the cause of the onset of the pains only if the elongated styloid process is left un-resected when the tonsillectomy is performed.

Evidently the involution changes that take place in connection with ageing may cause the onset of the pains. One such change is certainly discus degeneration of the cervical vertebrae which shortens the cervical spine and alters the position of the styloid process.

It seems that a similar state of pain may occur for other reasons without any contribution from the styloid process, or also that even a very short styloid process of incorrect shape or in incorrect position may cause the same symptoms. A division into paresthetic, neuralgic and cervical types (Wayoff, 1960) is too artificial. There are no clear boundaries between different types.

Because of the difficulties of differential diagnosis with respect to chronic tonsillitis, the tonsil pouches should never be left unpalpated, and any prominent styloid processes should never be left unremoved in connection with the tonsillectomies of older patients. Likewise, in doubtful stylalgia cases it is easy after a tonsillectomy to ascertain the presence of any styloid processes. If an operation is once resorted to the symptomless styloid process must also be resected in two-sided cases.

Finally I should still like to point out that stylalgia should be removed from the shelf of curiosities and introduced into the textbooks of otology Once the general practitioners learn to recognise the syndrome there will be no lack of cases.

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DISCUSSION

H Myrhaug In the literature there are occasionally referred cases of this kind where different pains about th head and neck and ears are ttributed to an elongated styloid process.

Stylalgia or pain caused by an longated styloid process occurs mainly after tonsillectomy (2,3) or following trauma (5) and by deviation of the tip f the process (1). Th symptoms may be similar t those found in the jaw dysfunction syndrome d in fact Costen s syndrome, which is synonym, is also mentioned as the most frequently encountered differential diagnosis (4).

In jaw dysfunction cases there are occasionally also pain in the throat, mostly unilateral, and the pain is located t the anterolateral part of the throat and t the region of the angulus of the mandible This pain is ttributed t the fact th t portion of the superior pharyngeal constrict muscl attach to the inner surface of the mandible (mylohyoid line). In the jaw dysfunction yndrome there is more or less displacement of the mandible, and th symptoms therefore seem t arise a consequence of muscular stress. — In cases of stylalgia it would be wise t examine th dental stat as well and evaluat displacement or deviation of the mandible as relief of pain in the throat is found following restauration of faulty bite Though the lecturer seems to ha great success in treatment of his patients.

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A COMPARISON BETWEEN THE FIBRES OF THE PERIODONTAL MEMBRANE AND THE FIBRES OF THE ANNULAR LIGAMENT IN THE OVAL WINDOW

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The author describes the fibers of the periodontal membrane which hold the teeth in proper position but still allow a certain movement and slight oscillation of the teeth during biting and mastication. He compares this system of suspension of the teeth with the arrangement of the annular ligament in the oval window, the membrane which keeps the stapedial footplate in its position. The excursions of the parts (tooth and stapes), the difference in force applied and in the histology of the structures in question, is mentioned.

This investigation is based on the following observations. Unilateral bony swelling of maxilla seems, in cases observed by the author (see p. 289), to originate in the region of a solitary (malerupted) and heavy loaded molar tooth. — The spongious deformity of bone in cases of otosclerosis seems to originate in connection to the stapes.

Both structures, tooth and stapes, constitutes moveable parts, fastened to their bony environment by fibrous ligaments.

The histology of both lesions (fibrous dysplasia and otosclerosis) show certain conformities (Fig. 1a & b). The author therefore find a good reason to investigate and compare the structure of the attachments of the parts concerned.

The natural proporions of a premolar of maxilla and the stapes is shown on Fig. 2. The mean length of the tooth is 25 mm and that of the stapes is 3 mm. The tooth and the stapes also have that in common that they do not grow or add

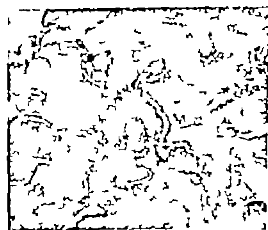


Fig. 1 a

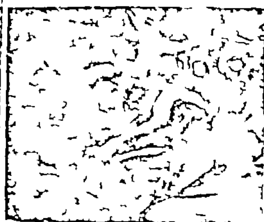


Fig. 1 b

Fig. 1. a) Fibrous dysplasia of maxilla. b) Otosclerosis. The anterior part of the footplate near the lower right corner. — An even distribution of fibrous tissue is seen in both pictures.

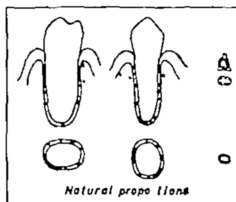


Fig. 2.

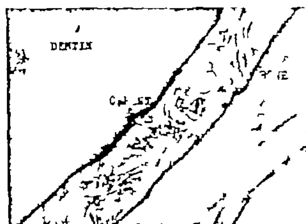


Fig 3. Periodontal membrane filling the space between the root f the tooth (cementum) and the jaw bone.

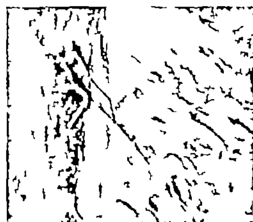


Fig 4 Oxytalan fibres (see arrows) entering th cementum.

in volume as do other bones, but stay the same size as the anlage at the time of birth and development indicate.

The biting force is between 3—9 kg (1) in the molar region. The rootfibres of tooth adapt to the functional stress and therefore the periodontal space varies

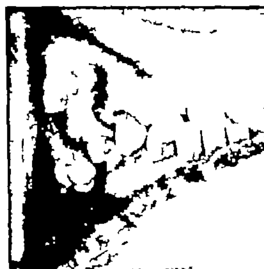


Fig. 5 a



Fig. 5 b

Fig 5 a) Prominences of bone at the sit heavy loaded teeth b) More extensive thic kening of the jawbone round the solitary molar

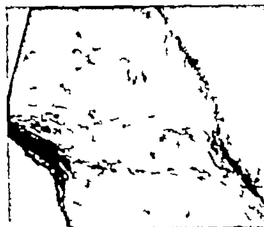


Fig. 6 Annular ligament, anterior part. Orcein stained Elastic fibres ppear blak. ×105.

from 0 08 mm in impacted teeth to 0.38 mm on teeth in function. This however has no bearing on the length of the periodontal fibres as they have different direc tions and are splitting up in branches like a meshwork. When the tooth is not loaded, the fibres have a wavy course. This implies that the tooth have a certain mobility as the fibres are stretched when the tooth is loaded.

The movement of the tooth as well as of the stapes during physiological conditions can hardly be seen by the naked eye. Estimation of normal tooth mobility has been done by several authors (1 14 16). The rate of normal chewing thrusts is found to be about 72 pr min. and the mean interval of chewing thrusts was 0 412 sec. Observations show that a tooth tends to remain in a certain displaced position in its socket during normal chewing except for the first fast phase of recovery The excursion of a front tooth is found to be 0 15 mm with a loading



Fig. 7 a. Fig. 7 b

Fig 7 Annular ligament,) anterio b) posterior part. Gomori aldehyde fuchsin (oxy talan stain). ×105. Elastic fibres ppea black.

of 1 kg in the horizontal plane (16) and distortion of the alveolar bone plate has also been demonstrated (14).

The fibres of the periodontal membrane consist of white collagenous connective tissue *They extend from the cementum of the root to the alveolar wall and are* seen to pass about 100 microns into the bone (19) (fig 3). With a special staining method, Gomori's aldehyde fuchsin, the collagen fibres take a green colour and with great magnification, some violet fibres can be distinguished (Fig 4) These are the oxytalan fibres described by Fullmer (1958) There are different opinions as to the character of these fibres (10, 13). They possibly represent a type of elastic tissue (4 6), and it is interesting to note that similar staining is observed on fibres of the annular ligament of the stapes, as will be mentioned later (Fig 7)

When a tooth is heavily loaded, destruction of the fibres of the periodontal membrane may be seen. But on moderate stress of a separate tooth, a thickening of the alveolar bone on the buccal side of the tooth may be observed (Fig 5a) and in some instances a more extensive thickening of the whole alveolar process occur at the site of a solitary tooth (Fig 5b). This seems to be an adaptation of the bone to the mechanical stress.

The connection between the stapes and the oval window have the characteristics of an articulation, the stapedio-vestibular joint as the rim of the footplate as well as the frame of the oval window are both covered with cartilage (Fig 6 7). The annular ligament is built up of both collagenous and elastic connective tissue fibres. The anterior part of the ligament is broader than the posterior part, which is acting as a hinge on which the stapes is moving, e.g. on contraction of the stapedial muscle.

The movement of the stapes is limited by the annular ligament to about 0 1 mm (5) but under physiological conditions, under the impression of sound, the

excursions are far less. For a constant eardrum pressure of 1 dyne pr.sq cm. the movement of the stapes is found to be 7/1000 mm at 125 Hz (5)

Special staining is needed to demonstrate the elastic elements of the annular ligament. By orcein staining one have the impression that the outer fibres only being of the elastic type (fig 6) while the inner and deeper layer stain as collagenous fibres By Gomori s staining method an interesting phenomenon is observed as the fibres of the posterior part of the ligament is staining yellow while fibres in the anterior part stain green, as did also the fibres of the periodontal membrane (Fig 7) In young individuals the elastic fibres are more abundant and it is also observed that the elastic fibres stain in the same way as do oxytalan fibres in the periodontal membrane and that they pass about 100 to 150 microns into the cartilage

How the collagenous fibres attach to the cartilage is uncertain, as they elsewhere in the body are calcified in their connection to bone substance. — This and other problems has to be subject to further study

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ENDONASAL SURGERY OF THE LACRIMAL PASSAGES.

DACRYOCYSTORHINOSTOMY AND CANALICULORHINOSTOMY WITH INTUBATION

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Rhinologists should tak part in lacrimal surgery Personal experience is decisive the uthor' rat of good results from dacryocystorhinostomy rised from about 60 per cent during the years 1940—47 to about 95 per cent. Som important d tails are stressed. — Intubation f the lacrimal passages should be used on limited d trong indications only (failure by dacryocyst rhinostomy persisting after revision, real canaliculostenosis, some posttraumatic conditions or congenital malformations). Th t be has been fixed using a ew m thod.

Published reports have indicated that good results have been obtained in about the same percentage of cases by external and by endonasal *dacryocystorhinostomy* in dacryostenosis with or without cystitis. Nevertheless, it is necessary that rhinologists take an active interest in surgery of the lacrimal passages since fairly few ophthalmologists consider themselves qualified to do this surgery and since the nasal approach is preferable to the external one in certain cases, in septal deviation of disturbing degree, hypertrophy of the middle turbinate, phlegmonous dacryocystitis, and above all when a revision proves necessary after failure of dacryocystorhinostomy

On the basis of 275 endonasal dacryocystorhinostomies, I feel convinced that a great deal of practice and experience is needed for good results to be obtained by this operation. While my first series of 58 operations during the years 1940—47 yielded only 59 % good long-term results, the corresponding figure for the later operations has kept at about 95 %. It should be noted, however that revision (usually simple removal of granulations) is required in about 15 of all cases after the primary operation.

Canaliculorhinostomy combined *with intubation* provides a valuable adjunct to surgery of the lacrimal passages. The operation can be successful also without intubation but it then mostly requires long aftertreatment by means of probing, and is therefore a strain on both patient and surgeon.

Intubation of the lacrimal passages should only be performed after evaluating the indications judiciously because the tube sometimes becomes a considerable mechanical load on the lacrimal puncta, which may be cleft to an undesirable extent. I have never performed intubation before first creating a high communica tion from the lacrimal sac or the canalicular system to the nasal meatus In some cases this communication had been created earlier for dacryostenosis and the intubation later proved necessary because of failure of the first operation. In cases of atresia of the canalicular system or the upper part of the lacrimal sac, the communication to the nasal meatus and the intubation were performed in the same sitting In my iew it is not advisable to insert a tube in cases of

dacryostenosis without first doing a dacryocystorhinostomy and, when needed, even a revision When doing so intubation is very seldom required in dacryostenosis.

The following are the main indications for intubation of the lacrimal passages.

1 Congenital atresia of the canalicular system or/and aplasia of the lacrimal sac.

2. Posttraumatic atresia of the canaliculus inferior the canaliculus communis, or of the upper portion of the lacrimal sac.

3 Failure of dacryocystorhinostomy and of subsequent revision.

Following the introduction, by Gröndahl in Norway of a hollow probe with a longitudinal cleft for insertion of the tube (Acta Ophthalmologica *41* 255, 1963), intubation of the lacrimal passages is now technically a fairly easy procedure Our technique is as follows.

One canaliculus is first dilated until a Bowman s probe No 3, which has proved sufficient, is passed Gröndahl s probe is inserted into the nose through the created high communication and through the probe a thin and soft polyethylene tube Portex 45 which is drawn out of the nostril. The probe is withdrawn The other canaliculus is then dilated, Gröndahl s probe is inserted, and the other end of the polyethylene tube is pushed into the nose, and similarly drawn out through the nostril The probe can now — and this is what is peculiar to Gröndahl's invention — be withdrawn so that the tube slips out of the probe through the cleft.

Gröndahl, who uses intubation in dacryostenosis without a previous dacryocystorhinostomy fixes the inserted tube as follows: its both ends are tied together by several knots so that the knots lie just inside the nostril This fixation which appears rather insecure is particularly unsuited if as is the case in our procedure the ends of the tube are inserted into the nose through a surgically created opening at the level of the upper portion of the lacrimal sac.

The fixation of the inserted tube is of very great importance as irritation may be caused by movement of the tube across the eye bulb in one of our first cases even erosion of the cornea ensued During a discussion of this problem, one of our nurses, Mrs Pääskynen came upon an ideal solution which to our knowledge was a new one: a piece of thicker polyethylene tube Portex 2, is threaded over both ends of the inserted thin tube and pushed high up into the nose until the thin tube lies in fixed position, forming a suitable curve between the lacrimal puncta (figures 1 and 2)

At the time, late in 1964 we thought that the described mode of fixation had not been used earlier Immediately prior to this congress we were informed that Dr Kivlranta at the Univerity ENT-hospital in Helsinki had adopted this method 40 days before us. The priority therefore belongs to him

Gröndahl s probe and the described mode of fixation have, according to our opinion, proved the solution to the technical problems of lacrimal intubation

The tube can be left in place without inconvenience to the patient, and it is removed after 2—5 months. Its removal is very easy the tube is sectioned between the puncta and withdrawn through the nostril.

Canaliculorhinostomy with intubation fails to give good results in some cases, partly perhaps because of the mechanical load on the lacrimal puncta. Nine of

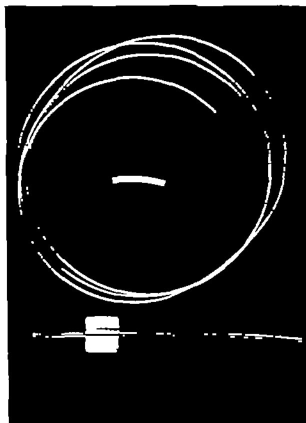


Fig. 1 Equipment required for lacrimal intubation. Gröndahl's hollow probe with a cleft, a soft polyethylene tube, Portex 45 for int bation, and piece of larger tube Portex 2, for endonasal fixation.

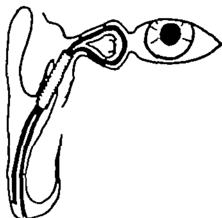


Fig. 2. The t be inserted and fixed in position.

our 12 patients became asymptomatic, which can be considered satisfactory in view of the fact that we did not use the procedure unless very definitely indicated, in particularly difficult cases.

Gröndahl s probe, as far as we know is not commercially available. We obtained ours by placing an order with Gröndahl s own manufacturer Ellert Olsen Erlevn 51, Bergen, Norway

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RESTORING THE PATENCY OF OBSTRUCTED LACRIMAL PASSAGES ON DACRYOCYSTORHINOSTOMIZED PATIENTS

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Three simple method for tubing of blocked or torn lacrimal passages, requiring no special instruments, are described.

In connection with the corrective operations of traumatic or postoperative dacryostenosis a plastic tubing is often used. Concerning canalicular stenosis the use of such a tube may be a method of choice.

The related methods where a plastic tube or corresponding thing is threaded through the lacrimal passages are quite intricate. Special instruments and in most cases high-degree dilatations of the tearducts are necessary. Besides, when using these methods the end of the tube or thread may stay in the inner canthus irritating the conjunctiva or turning the lid into ectropion.

Since 1961 prolonged intubation without these disadvantages has been used in several tens of cases at the ENT department of the Helsinki University Central Hospital.

The operation is begun with West's endonasal dacryocystorhinostomy if not performed before. As indwelling catheter is generally used Teflon® (tetrafluorocarbon) tube, outer diameter of which by inner diameter is 0.5×0.8 mm. In some heavily scarred canalicular stenoses a tube of 0.9×1.4 mm has been used.

The ends of a piece of tube of about 20 cm's length are tapered by pulling on over the flame of a spirit lamp. For better lacrimal drainage a minute window is pared away in the middle of the tube as fenestra novovalis in fenestration operation. The spring, »memory« of the tube in the immediate vicinity of the window must be softened in the same way over a flame or in boiling hot water.

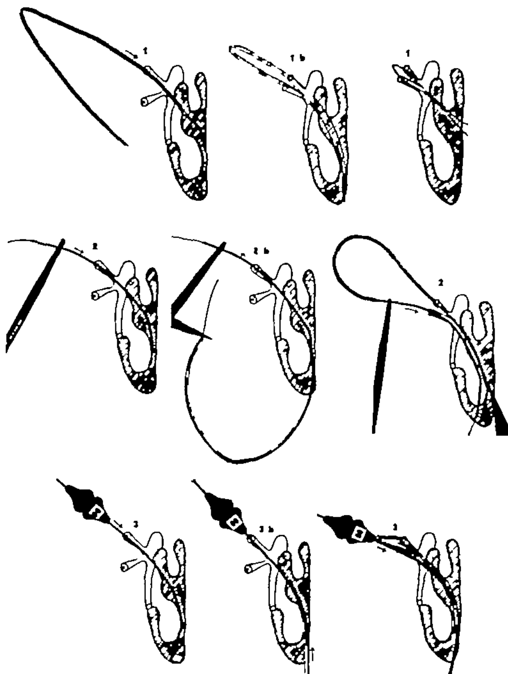
If Bowman's probe no. 1—0 or 2—0 is easily passed into the nose the simplest method is used.

Method I

The one of the tapered tube ends is passed from the upper punctum, the other one from the lower punctum into the nose like a lacrimal probe (figures 1 a and 1 b).

The plastic tube can be stiffened into a probelike instrument with a steelwire passed through its bore.

A thin Teflon® tube being used it is generally easy to push along the cleared pathways even without any tools or taperings; however, the most often practiced method is the following one.



Figures 1, 2 and 3. Methods I, II, and III described in the text.

Method II

The mount of a fine-gauge hypodermic needle is cut away and the cannula portion is bend. Inside this blunt, curved needle without mounting a nylon string or steel wire is threaded. The needle is passed from the upper lacrimal punctum into the nasal fossa (fig. 2 a).



Figures 4 and 5. Radiograph of a thin T flon tube in situ with the bushing in the lacrimal sac front and side view
(Contrast medium being faintly identifiable in thin plastic tube in these pictures a steel wire was left in the tube lumen I the end the course of the steel wire has, in addition, been outlined in white India ink.)



Figure 6. Plastic tube in inner canthus is fairly invisible even when the patient is gazing laterally

The bodkin end of the nylon filament (or steel wire) is catched in the nasal cavity led out through the nostril, and the nicked plastic tube is threaded on it. The tube and the thread inside it are clamped together above the window by a mosquito clamp Traction on the upper end of the nylon string will bring the needle together with the tube through the upper canaliculus and punctum (fig 2 b)

The needle is now shifted to the beforehand probed lower punctum and along the needle the plastic tube is driven through the lower canaliculus into the nasal fossa (fig 2 c). While tackling that the tube and the thread are clamped together underneath the tube window

Method III

When the space between the puncta and the rhinostomy is heavily scarred or crooked it may be necessary to use the lacrimal probe as a stylet (mandrin) in passing the tube via both canaliculi. The upper canaliculus being thinner it is

easier to insinuate the tube from the rhinostomy into the upper canaliculus than vice versa For that purpose a tiny probe is introduced through the upper punctum in the nasal fossa (fig. 3 a), and the tube is threaded on it (fig. 3 b). The tube and the probe are clamped together and pulled through the bony ostium along the canaliculus into the palpebrale fissure (fig 3 c). The probe is now shoved from the tube and shifted through the tube window to the other fork of the tube and pushed via the lower canaliculus through the block into the nasal cavity

The free ends of the indvelling tube are pulled downwards in order to bring the tube window between both puncta. The tube is secured to the optimal position by stringing an 1 cm long plastic tube bit of a little greater caliber on the both tapered tube ends. This plastic bushing is pushed to the lacrimal sac level by means of an alligator forceps (fig 1 c) The purpose of this bushing is furthermore to ensure the maintainance of larger patency at the bony ostium. Finally the nasal ends of the tube are cut down at the level of the inferior turbinate.

The tubing may be prolonged for three to six months. In one by the patient neglected case this was continued for a year and a half without any deletarious effects, and with good lasting result.

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CYTOLOGIC DIAGNOSIS ON ASPIRATE FROM 1000 SALIVARY-GLAND TUMOURS

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Cytologic reports from aspiration biopsy in 1000 salivary gland lesions have been compared with clinical and histological observations.

The cytologic reports on the aspirated material yielded a positive tumour diagnosis in roughly 92 % of the cases with histologically verified tumours. In addition to simple confirmation of tumour presence information concerning the histologic type of tumour was obtained in about 0% of the material. The main reason for this lower figure was difficulty in recognizing cystadenolymphoma and the malignant variants of the salivary gland tumours. After a morphologic study of smears from cystadenolymphoma we have been able to increase our accuracy in diagnosing this type of tumour. The possibility of recognition of the malignant salivary gland tumours by cytologic technique is discussed.

Localized swelling of a salivary gland may be caused by a neoplasm, cyst, unspecific or specific lymphadenitis, sialolithiasis, sialoadenitis or systemic disease. Physical examination, laboratory tests and sialography gives some guidance in the often difficult matter of a differential diagnosis. Surgical biopsy or biopsy with such a large-bore needle that a tissue specimen is obtained for histologic diagnosis should not be done, particularly when a major salivary gland is involved. This is because an intervention of this kind involves a fairly great risk of spreading tumour cells.

Fine-needle biopsy, i.e., aspiration biopsy with a fine-bore needle (maximum outer diameter 0.7 mm), produces less trauma than other biopsy methods. Moreover, the risk of spreading tumour cells in the surrounding tissue seems to be minimal.

The fine-bore needle is attached to a 10-ml syringe of Luer Lok type. The syringe has a special handle which allows a one-hand grip during puncture (Franzén, Giertz and Zajicek, 1960). The other hand can then be used to steady the relevant organ. The aspirated material is spread on a glass slide. Since only individual cells or small aggregates of cells can be obtained, the method is denoted as cytologic puncture diagnosis.

Although, hitherto, routine use of cytologic puncture biopsy has generally been confined to haematology, in recent years it has been increasingly applied in tumour diagnosis as well (Söderström, 1966). Thus, at Radiumhemmet 1000 puncture biopsies of salivary glands were made in 1953—1965 when a tumour was suspected. However, as far as salivary-gland tumours are concerned, cytologic diagnosis has met with great difficulties — especially up to the early 1960's — in view of the lack of any uniform, generally accepted histologic classification. Subsequently a classification was introduced in which tumours of the salivary glands are divided into histologically well-defined types. This implies that a basis

was created for the development of cytologic puncture diagnosis of salivary-gland tumours also As a first step in this development, we reviewed our material of punctured salivary-gland tumours, and correlated the cytologic diagnoses with the histologic findings, classified according to modern nomenclature (Foote and Frazell, 1954)

In 690 of the 1000 cases of puncture biopsy (i.e., in more than 2/3 of the whole material) the cytologic diagnosis could be correlated with the histologic one since operation had been performed The chief reason why operation was not undertaken in the remaining cases was that no tumour cells were demonstrable at cytologic examination, and the clinical picture was rapidly normalized there after In a few cases, operation was not performed despite the observation of tumour cells at cytologic examination. The reason was either that the patient refused operation, or that the tumour was regarded as inoperable.

Table 1 shows the site of the 690 operated lesions of the salivary glands in which the cytologic diagnosis could be correlated to the histologic one. It is seen that there was a large preponderance of lesions of the parotid gland — 604 of 690 cases — whereas the submandibular gland was involved in 69 the sublingual gland in 3 and minor salivary glands in only totally 14 cases.

TABLE 1

Site of lesion	No tumour	Metastasis	Recurrent tumour		Primary tumour		Total
			benign	malignant	benign	malignant	
	74	23	51	40	413	89	690
Parotid gland	54	11	45	32	390	72	604
Submandibular gland	19	11	6	5	17	11	69
Sublingual gland	1	—	—	1	1	—	3
Minor salivary glands	—	1	—	2	5	6	14

The histologic examination showed no tumour in 74 cases, metastasis to a salivary gland from other sites in 23, and local recurrence of a tumour in 91 (benign in 51 and malignant in 40) In 413 cases examination disclosed a benign primary tumour and in 89 a malignant primary tumour

In almost all 74 cases in which no tumour was found at histologic examination, the cytologic and histologic diagnoses agreed. This group consisted mainly of such lesions as sialoadenitis, lymphadenitis and cysts.

All 23 cases of metastasis from another site to a salivary gland were diagnosed cytologically as carcinoma of various types. This was due chiefly to the fact that the primary tumour was known in about 90 % of the cases, so that the expected cytologic features were fairly easily identified

A correct cytologic diagnosis was made in 86 of the 91 recurrent tumours i.e., in about 95 %.

The matter of greatest interest is, however the reliability of cytologic diagnosis in the primary salivary-gland tumours.

This reliability was investigated by a correlation study between the cytologic and the histologic diagnosis of these tumours. It must, however be emphasized

that the former diagnoses are the original ones, whereas the latter were established after histologic re-classification of the material according to modern nomenclature.

Table 2 shows the results of this correlation study in 413 primary benign tumours of salivary glands.

TABLE 2

Cytologic findings	Histologic findings				Total
	Cystadeno-lymphoma	Onco-cytoma	Benign mixed tumour	Benign mesen-chymal tumour	
	52	3	346	12	413
No tumour cells or unsatisfactory specimen	21	—	9	3	33
Tumour cells, classification not possible	1	—	15	—	16
Cystadenolymphoma	22	—	—	—	22
Oncocytoma	5	3	—	—	8
Tumour probably benign mixed tumour	—	—	12	—	12
Mixed tumour benign	1	—	308	—	309
Mesenchymal tumour	—	—	—	9	9
Carcinoma cells	2	—	2	—	4

In 17 cases malignancy was suspected.

In 33 of these 413 cases, no tumour cells were identified cytologically. This implies that cytologic examination failed to disclose the tumour in about 8 % of the cases.

In a study of each type of benign tumour separately, highly satisfactory agreement can be noted between cytologic and histologic diagnosis, with the exception of papillary cystadenolymphoma. Thus, a correct cytologic diagnosis was made in all 3 cases of oncocytoma, in 320 of 346 mixed tumours and in 9 of 12 mesenchymal tumours. On the other hand, only 22 of 52 papillary cystadenolymphomas had been correctly diagnosed cytologically, whereas in 21 of the remaining 30 only cystic contents with a few cells were observed. These cells — denoted as oncocytes — have, however, proved to be characteristic precisely of papillary cystadenolymphoma. By means of morphologic studies on smears of cells aspirated from this type of tumour, we have been able to increase the accuracy of cytologic diagnosis in papillary cystadenolymphoma from 21 % in 1953—62 to over 80 % in 1963—64 (Eneroth and Zajicek, 1965).

This improvement does not only imply that cytologic diagnosis of the various types of benign salivary-gland tumours has by now attained a high degree of reliability. It also implies that, nowadays, the existence of a benign salivary-gland tumour of any kind seldom escapes detection at cytologic examination.

With respect to the *primary malignant tumours*, table 3 shows the cytologic findings in the various types, when the material was re-classified according to modern nomenclature.

As far as the reliability of cytologic examination to disclose the existence of a tumour in general is concerned, it is seen that 8 of 89 malignant salivary-gland tumours (about 9 %) were not diagnosed correctly, but were denoted as cysts. Seven of these 8 cases belonged to the group of mucoepidermoid carcinoma; thus,

TABLE 3

Cytologic findings	Histologic findings							Total
	Malignant mixed tumour	Mucoepidermoid carcinoma	Adenoid cystic carcinoma	Acinic cell carcinoma	Adenopapillary carcinoma	Anaplastic carcinoma	Malignant mesenchymal tumour	
	5	18	23	25	4	8	6	89
Cystic contents	—	7	1	—	—	—	—	8
Benign tumour	1	3	13	11	3	1	—	32
Suspected malignant tumour	1	1	3	2	1	1	—	9
Carcinoma	3	7	6	12	—	6	1	35
Mesenchymal tumour	—	—	—	—	—	—	5	5

the existence of a tumour could be established cytologically in only 11 of these 18 tumours. In other tumour types, the presence of tumour cells was demonstrable cytologically in every case, apart from one of adenoid cystic carcinoma.

It is apparent from table 3 that little attempt was made to diagnose the type of tumour cytologically but that the tumour cells were chiefly denoted as benign, of suspected malignancy or as malignant. This is because at the primary cytologic examination of the material — up to the early 1960's — possibilities of clearly defining the various types of malignant tumour were also lacking histologically. This circumstance explains why cytologic examination even failed to establish malignancy in relatively many cases. Thus, of the 81 malignant salivary-gland tumours in which tumour cells were found, only 44 — i.e., about 54% — were evaluated cytologically as malignant or of suspected malignancy.

On the basis of morphologic studies on cell smears from various types of malignant tumours, we have succeeded in recent years in achieving a high degree of accuracy in identifying, e.g., adenoid cystic and acinic cell carcinoma, which have characteristic cytologic features. We hope that we will be enabled in the near future — by means of further morphologic studies of cell populations in other malignant tumour types — to attain as great accuracy in the cytologic diagnosis of malignant tumours as that we have already achieved in benign tumours of the salivary glands.

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DISCUSSION

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On careful analysis of cases of parotid tumour treated at Karolinska Sjukhuset Eneroth found that so-called satellit tumour had occurred in connection with recurrences after previous operation and in 3 cases in which puncture biopsy had been performed. I should like to ask Dr. Zajicek wh ther puncture biopsy may cause a local spread of t mour.

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EINIGE BEOBACHTUNGEN ÜBER DIE SPURENELEMENTE DER TONSILLEN

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(Vorstand. Prof. Dr. med. Otto H. Meurman)

Mit spektrographischen Methoden hat man versucht sowohl qualitativ als auch quantitativ das Vorhandensein der Spurenelement in Gaumenmandeln zu erläutern. Die Analyse wird aus den Tonsillenaschen von 36 Patienten durchgeführt und die Untersuchung wurde auf 26 Metalle begrenzt. Von diesen waren 10 (Al, Ca, Cu, Fe, Mg, Mn, Na, Pb, Sn, Zn) in jeder Probe. 4 (Ag, Cd, V, Ni) nur in einigen Proben. 6 Metalle hatten konstant Menge (Al, Cu, Fe, Mg, Mn, Na), während acht (Ag, Ca, Cd, Ni, Pb, Sn, V, Zn) variierende Menge hatten. Man konnte keine Korrelation zwischen dem Geschlecht und der Menge und dem Vorkommen eines Metalls feststellen, das einzige zu dessen Menge das Alter deutlich beitrug, war Calcium, dessen Menge mit dem Alter zunahm.

Die anorganischen Grundstoffe, die im menschlichen Organismus vorkommen, lassen sich in Haupt und Spurenelemente auf Grund ihrer Erscheinungsmenge teilen, während der Höchstbetrag der letzteren 0.01 % vom Gewicht des Trockenstoffs steigen darf. Von der Bedeutung der Spurenelemente sind recht verschiedene Meinungen hervorgebracht worden und recht lange ist die Frage offen gestanden ob die Metalle im menschlichen Organismus meistens nicht nur auf Durchreise sind, wenn sie sowohl im Boden als auch im Pflanzenreich vorkommen (Berg 1940). Heute ist es schon bekannt, dass die anorganischen Verbindungen lebenswichtig sind und wir können auch den grössten Teil von ihnen in verschiedene Funktionen hinstellen und sie entweder auf Grund ihrer Menge oder der Funktion in verschiesenen Gruppen einteilen. Ausser als Baumaterial in Geweben haben die Minerale ihre Funktionen in kolloid-chemischen Zuständen, beim Erhalten des osmotischen Drucks und in fermentativen Vorgängen.

Dessen ungeachtet dass die Minerale im Organismus heute Objekte einer recht regen universalen Erforschung sind, ist als ein ziemlich unerforschtes Gebiet das lymphoepitheliale Gewebe und besonders der sog. Waldeyersche Rachenring zu erwähnen, dessen Spurenelemente in Tonsillae palatinae diese Forschung sowohl qualitativ als auch quantitativ mit spektrographischen Methoden zu erläutern versucht

Erforschungsmaterial und Methode

Das Material besteht aus entfernten Gaumenmandeln von 36 Patienten. Die Patienten sind nur in der Beziehung erwählt worden, dass man ihr Alter in möglichst viele Altersgruppen einteilen konnte (Tabelle 1)

Nach der Tonsillektomie wurden die Gaumenmandeln in mineralfreie Quarztiegel hingestellt, die in einen Thermostat von 110°C in 24 Stunden verlegt wurden um

TABELLE 1

MATERIAL. ALTERS- UND GESCHLECHTSVERTEILUNG

Alter	Männer	Frauen	Total
–10	4	2	6
11–20	2	4	6
21–30	2	3	5
31–40	3	5	8
41–50	3	4	7
51–60	2	1	3
61–70	–	1	1
Total	16	20	36

TABELLE 2

DIE ERFORSCHTEN ELEMENTE, IHRE WELLENLÄNGEN UND VORKOMMEN IN PROZENT

Die erforschten Elemente und Wellenlängen Å	In jeder Probe	In einigen Proben	Konstant Grösse %	Variierende Grösse %	Nur Spuren ~
Ag 3280.6		+			0–~
Al 3082.1	+		0.001		
As 2349.8					
Au 2427.9					
Be 2348.6					
Bi 3067.7					
Ca 3179.3	+			0.001–1.0	
Cd 2288.0		+			0–~
Co 2521.3					
Cr 2843.2					
Cu 3247.5	+		0.001		
F 2679.0	+		0.1		
Ga 2874.2					
Ge 2651.1					
In 3039.3					
Mg 2852.1	+		1.0		
Mn 2794.8	+		0.001		
Mo 3132.5					
Na 3302.3	+		>1.0		
Ni 3050.8		+		0–0.1	
Pb 2833.0	+			~–0.01	
Sb 2598.0					
Sn 2839.9	+			~–0.01	
Tl 3372.8					
V 3183.9		+			0–~
Zn 3302.5	+			0.01–1.0	
26	10	4	6	5	3

die Flüssigkeiten verdunsten zu lassen. Als durchschnittliches Trockengewicht erhielt man 1.6923 g. Die Verbrennung geschah in einem elektrischen Ofen während 3 Tage, wobei die Wärme allmählich zu 480°C erhöht wurde. Das Aschengewicht war durchschnittlich etwa der 12.5. Teil vom obenerwähnten Trockengewicht. Als die anorganischen Grundstoffe so übriggeblieben waren, wurde aus der so erhaltenen Asche eine spektrochemische halbquantitative Analyse durchgeführt. Hier strebte man nicht nach eigentlicher Analysegenauigkeit, sondern man hatte das Ziel, die Menge der Spurenelemente und ihre relative Menge einander gegenüber klarzumachen.

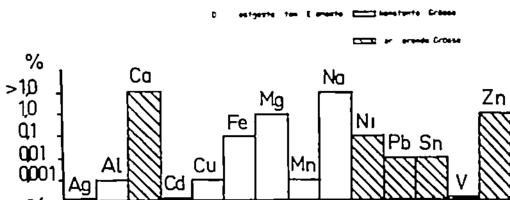


Fig. 1

In der Forschung wurde der Quarzspektrograph von Hilger gebraucht, in dem die Graphitelektrode Ringsdorff RW spectral IV und Plattenart Ilford half tone plate. Die Asche wurde in eine Graphitelektrodeschale 5.5×4.8 mm hingestellt Die Amperezahl des Gleichstromlichtbogens 14 Ampere der Wechsel ± 0.5 Ampere. Die Distanz der Elektroden 5 mm, der Winkel 120° Als Blendescheibe eine drehende Scheibe durch deren offenen Sektor 15 % vom Licht auf die Prismen des Spektrographs kam. Die Breite der Öffnung 0 03 mm und die Höhe des Spekt*rums 2 mm. Wellenlängegebiet 2 500—3 650 Å. Die quantitative Bestimmung in* Komparator durch Vergleich von Spurenelementproben die eine bekannte chemische Verbindung und Grundstoffe hatten

Es ist bekannt, das die Spektralanalyse erheblich schwieriger durch die begrenzte Menge des zu erforschenden Materials wird Um die Analyse leichter zu machen hat man auch die Grundstoffe, die man erforschen wollte auf 26 begrenzt die so erwählt worden waren, dass ihre Spektrallinien möglichst wenig einander störten (Tabelle 2).

Resultate

Von den erforschten Elementen stellte man fest, dass 14 in Tonsillenaschen vorgekommen waren (Tabelle 2 und Fig. 1) und von diesen folgende 10 in jeder Probe Aluminium, Calcium, Kupfer Eisen, Magnesium Mangan, Natrium, Blei, Zinn und Zink, Silber Cadmium und Vanadium — nur Spuren — sowie Nickel in einigen Proben.

Konstante Menge hatten Natrium > 1 %, Magnesium 1 %, Eisen 0 1 Aluminium, Kupfer und Mangan 0.001 %. Varierende Menge hatten Calcium 0.01→1 0 % und Zink 0 01—1.0 %. Nickel 0—0 1 / sowie Blei und Zinn ~ —0.01 %. Man konnte keine Korrelation zwischen dem Vorhandensein der Metalle und dem Geschlecht feststellen Das einzige Metall, auf dessen Menge das Alter deutlich Einfluss hatte war Calcium so, dass die Menge mit dem Alter folgenderweise zunahm. unter 10 Jahren 0.001 %, 20—30 Jahre 0 01—0 1 % und von hier an allmählich über 1 vom erforschten Trockengewicht.

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SUBJECTIVE APPRAISAL AND OBJECTIVE ASSESSMENT OF THE HEARING OF SPEECH AMONGST A GROUP OF ADULTS WITH IMPAIRED HEARING

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A number of patients with impaired hearing consulting the E.N.T Dept. of Rikshospitalet were asked t appraise their hearing from general point of view and their hearing for speech in specified listening conditions. Data from 166 patients with median ge 55 years, coming from all parts of Norway representing 61 different occupations, with hearing loss within range of 20 dB at 500 through 2 000 Hz, and full discrimination on PB word lists, were selected. Good agreement existed between general appraisal and the sum of ratings for specified listening conditions. 37 per cent of the material rated their hearing as mediocre 63 per cent as poor As t hearing threshold for speech considerable overlapping existed between groups. Significant differences of threshold levels between ears increased, small ones reduced the difficulties caused by the same hearing loss for speech in the better ear Hearing threshold level for speech in better and worse ear was 33 dB and 45 dB in the mediocre, 45 dB and 60 dB in the poor hearing group. Good agreement existed between threshold level for speech and for pure tones t 500 through 2 000 Hz. Clinical conversational voice test was of no value in the individual case but median values of the material give information on the relation of hearing loss t hearing distance for speech.

35 dB hearing loss for speech, or Hearing Index 64, is proposed as lower limit for procuring of a hearing aid free of charge according to present Norwegian regulations.

Since modern pure tone audiometry was brought into use in the 1920-ies (16) it has been possible to compare hard-of-hearing individuals subjective appraisal of their hearing with the results of objective assessment. Beasley (1) in 1936 classified the types of hearing impairment into five groups with increasing difficulties in under standing everyday speech. The first three of his groups were as follows:

1 The individual has difficulty in understanding speech in church, at the theatre and in group conversation.
2. The individual has difficulty in hearing conversation at close range.
3. The individual has difficulty hearing over the telephone at ordinary intensities.

This classification according to the speech hearing capacity in the most important everyday listening conditions has been used by Silverman et al. in 1948 (13), and seems appropriate also today

In the large material from the U S. National Health Service hearing survey 1935—36 Beasley found the average hearing loss at 1024 and 2048 Hz to be 20—24 dB in the first grade, 40—45 dB in the second, and 65 dB in the third, when the grading was made according to information from the individual himself As Beasley s zero hearing level was based on audiometric examination of a large

number of »normal hearing« people the hearing levels reported may presumably be compared to those of the present study using Sivian and White zero hearing threshold level

Walsh and Silverman (15) stated in 1946 that »It is generally accepted that if an individual has a hearing loss for speech greater than 35 dB he is a candidate for a hearing aid »and that« 35 dB ± 15 constitutes the area of social adequacy »

From a study of 123 fenestrated patients Silverman et al (13) confirmed that more than 30 dB hearing loss for speech caused difficulties in understanding speech under everyday listening conditions, and if the loss was 35—60 dB the difficulties were considerable They found that »a very few patients who had one nearly normal ear wanted improved hearing in the worse« but, on the other hand that »selfrating in relation to hearing loss revealed an almost unbelievable degree of optimism» in a number of patients.

Under regulations of October 1964 the Norwegian State grants free hearing aids to a limited group of adults with impaired hearing to hard-of hearing parents with children under 20 years of age at home, in order to secure speech-hearing communication between children and their parents. The decision of who was entitled to benefit from this arrangement had, however to be based on objective criteria To establish such criteria a group of adults with impaired hearing consulting the E.N T Dept. were selected For this group procuring of free hearing aid had not arisen Through a questionnaire the patients were invited to appraise their hearing from a general point of view and in a number of specified listening conditions, as Good Mediocre or Poor Data from 166 patients could be used for the study Conductive hearing loss, with or without additional sensori-neural hearing loss was present in both ears of 153 patients, 139 of them having otosclerosis. In 13 patients the hearing loss was of pure sensori-neural type.

In the 332 ears the hearing threshold levels at 500 1 000 and 2 000 Hz were within a range of 20 dB In 57 per cent of the ears the threshold level was within the same range also at one or more of the frequencies 3 000 4 000 and 6 000 Hz, in 24 per cent at least 10 dB less and in 19 per cent at least 10 dB greater

All the ears showed a discrimination score of 90—100 per cent on PB monosyllabic word lists.

According to selfrating from a general point of view 62 patients, 28 men and 34 women i e. 37 per cent of the total, were of the opinion that their hearing was Mediocre, 104 patients, 48 men and 56 women, i e. 63 per cent that it was Poor

As it appears from Table 1 the general self-rating accords well with the sum of ratings in the specified listening conditions. The great number of no reply to theatre and cinema is not caused by hearing impairment only The rural population has usually no easy access to these entertainments. With omission for the no replies the distribution on good, mediocre and poor hearing in the specified listening conditions is for the group generally Mediocre 17 48 and 25 per cent respectively 9 27 and 64 per cent for the group generally Poor The table confirms the classification of Beasley Difficulties arises first in church at the theatre and in group conversation, then in conversation at close range, and at last in telephone.

TABLE 1

RELATION BETWEEN SUBJECTIVE APPRAISAL OF THE HEARING FROM A GENERAL POINT OF VIEW AND IN SPECIFIED LISTENING CONDITIONS

Listening condition	Hearing group							
	Mediocre N = 62				Poor N = 104			
	good	mediocre	poor	no reply	good	mediocre	poor	no reply
Close range, familiar	39	22	1		16	55	33	
unfamiliar	16	35	11		1	37	66	
Group conversation	7	21	34			11	93	
Church	3	30	25	4	1	9	89	5
Theatre	1	21	19	21		5	74	25
Cinema	7	22	13	20	1	19	41	23
Lecture	3	25	20	14		11	82	11
Radio	20	36	6		11	43	50	
Television	14	29	5	14	12	27	55	10
Telephone	37	23	1	1	40	45	17	2
Total	147	264	135	73	68	191	259	76
Per cent	24	43	21	12	8	25	60	7

Different social and occupational conditions make different demands on the speech hearing capacity as stated by Beasley The 166 patients comprised by the study came from all parts of Norway 46 per cent from towns and city-like places, 54 per cent from rural districts and villages, in fair accordance with the distribution of the general population, 49 and 51 per cent respectively

61 different occupations are represented by the 134 patients who provided information on this point. If Housewifes is considered an occupation, the percentage distribution on major occupational groups in the present material and in the general population is as shown in Table 2.

Agriculture, forestry etc. is markedly underrepresented, in agreement with the slight influence of hearing impairment on employment in this group stated by Beasley The insignificant preponderance of women in the general population taken into account, the housewives are considerably overrepresented in the material. For the actual study of speech-hearing communication ability between children and their parents this may be an advantage.

TABLE 2

PERCENTAGE DISTRIBUTION ON MAJOR OCCUPATIONAL GROUPS IN THE PRESENT MATERIAL N = 166, AND IN THE GENERAL POPULATION

Occupational group	Present material per cent	General population per cent
Agriculture, forestry fishing, whaling	5	13
Mining, manufacturing, construction etc.	23	24
Trade, finance transport	11	16
Services	10	12
Housewives	44	33
Others	7	2

TABLE 3

AGE DISTRIBUTION AMONGST MEN AND WOMEN AND THE GROUPS MEDIOCRE AND POOR HEARING

Age, years	Median	Mean	Mean deviation
76 men	5.	53.3	9 7
90 women	55	55.8	9.2
Total 166	55	55.5	9.3
Medi ocre N = 62	55	51.8	10.3
Poor N = 101	55	58 1	8.5

The age distribution of the material appears from Table 3. The median age is the same and the mean fairly even amongst men and women, but slightly higher in the poor hearing group than in the mediocre.

The hearing has been examined by monaural pure-tone and speech audiometry in sound-proof rooms with a background noise of 19—20 dB A, 33—34 dB C on a Brüel & Kjær sound level meter All ears are examined by means of PB monosyllabic word lists, 169 ears also by means of a three-digit test. The difference between the hearing threshold levels of the two tests was in 81 per cent of the ears 5 dB ± 5 as is often found even in normal hearing young adults.[1]

In case of difference between the threshold levels for the three-digit test and the PB monosyllabic word lists, the threshold for bisyllabic words (of spondee-like stress) will normally be situated between them In the present material it is therefore justified within a range of 5 dB to accept the threshold level for PB monosyllabic words as giving the »Hearing loss for speech»

Fig 1 shows the hearing threshold level for monosyllabic words in the better and worse ear in the groups mediocre and poor hearing

There is considerable overlapping between groups, as found by Silverman et al. It appears, however that significant difference between the ears seems to reduce the patients hearing capacity in his own opinion

Taking the 166 patients as one group of more or less hard-of-hearing adults, we may compare the hearing threshold level for speech in the better ear to the threshold level difference between ears as shown in Fig 2. The general trend of the curve appears also in the two subgroups, and shows that the smaller the difference between ears, the greater the hearing loss in the better ear and, conversely the greater the difference the smaller the hearing loss in the better ear Significant difference between ears increases, small ones reduces the difficulties caused by one and the same hearing loss for speech in the better ear This is in accordance with

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[1] *Foot-not* Norwegian speech udiometry has as zero hearing threshold level 35 dB rel. 0.0002 dyn/cm² t which the average normal listener (4) is able to repeat correctly 50 per cent f Norwegian monosyllabic PB words, corresponding to the 33 dB rel. 0.0002 dyn/cm² level reported by Davis for U.S. monosyllabic words.

Irrespective of the true hearing threshold level of th three-digit and bi-syllable word lists rel. 0.0002 dyn/cm² they have been given the same zero hearing loss level as th monosyllable word lists in order to get uniform dial readings of the hearing loss for the different kinds f speech test. All the word lists are equalized to uniform intelligibility threshold.

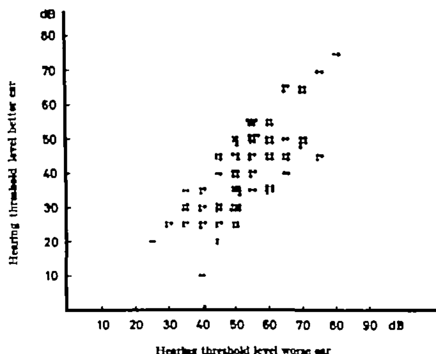
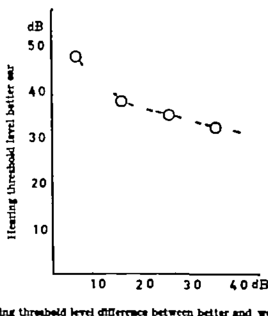


Fig. 1 Hearing threshold level of better and worse ear for PB monosyllabic word lists in the groups Generally mediocre ● and generally poor ★ hearing



Hearing threshold level difference between better and worse ear

Fig. 2. Hearing threshold level for PB monosyllable word lists in better ear in relation t differ ence between hearing threshold levels for BP monosyllabic w rd lists in better and worse ear N=166

previous reports on the advantages of dichotic hearing for the understanding of speech in everyday listening conditions (2, 6 8, 10 11 17)

The median and mean hearing threshold for PB monosyllabic words in the better and worse ear in the groups mediocre and poor hearing appears from Tab 4

TABLE 4

HEARING THRESHOLD LEVEL FOR PB MONOSYLLABIC WORD LISTS IN BETTER AND WORSE EAR BY MEDIOCRE AND POOR HEARING

Hearing group	Ear	Hearing threshold level dB for PB monosyllabic words		
		Median	Mean	Mean deviation
Mediocre N = 62	Better Worse	33 45	32 47	11 9
Poor N = 101	Better Worse	45 60	45 61	10 10

The median hearing loss in the better ear in the mediocre group is 35 dB in the poor hearing group 45 dB in fair accordance with the findings of Walsh and Silverman, and Silverman et al The mean hearing threshold level difference between ears is the same in the two groups.

The relation between hearing threshold level for PB monosyllabic words and the average hearing level at 500 1 000 and 2 000 Hz is shown in Fig 3. The hearing

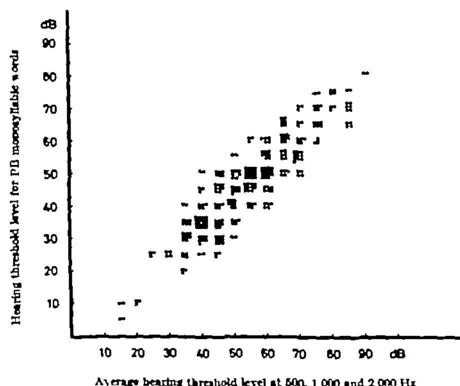


Fig. 3. Hearing threshold level for PB monosyllabic word lists in relation to average hearing threshold level at 500, 1 000 and 2 000 Hz N = 332 ears (Sivian and White ref. zero hearing level)

threshold level for PB words is on an average 9 7 dB lower than the average threshold level for pure tones. This is in fair accordance with the difference between the hearing threshold level in the »average normal listener» and in a selected group of motivated (paid) student listeners under optimal conditions (Cfr Chaiklin & Ventry p 49). 90 per cent of the observations are within ± 10 dB of this 9 7 dB difference. In the 24 per cent of the ears showing better hearing above 2 000 Hz than at 500 through 2 000 Hz the mean threshold level difference was 10 6 dB with mean deviation 5 7 dB, in the 19 per cent with greater hightone loss 4.2 dB with mean deviation 4.5 dB Though the correlation between speech tests and pure tone audiometry is by no means perfect (14), the present study shows a fair correlation as has previously been stated by others (5, 12, 14)

The median and mean average hearing threshold level at 500 1 000 and 2 000 Hz in the groups mediocre and poor hearing appears from Tab 5.

TABLE 5

MEDIAN AND MEAN VALUES FOR THE AVERAGE HEARING THRESHOLD LEVEL AT 500, 1 000 AND 2 000 HZ FO BETTER AND WORSE EAR IN THE MEDIOCRE AN POO HEARING GROUPS (SIVIAN ND WHITE REF ZERO HEARING LEVEL)

Hearing group	Ear	Average hearing threshold level dB ,500 – 2 000 H		
		Median	Mean	Mean deviation
Mediocre N = 62	Better	40	38.8	9.8
	Worse	60	53.9	11 6
Poor N = 104	Better	55	53.9	8.5
	Worse	65	65.2	8.3

If the ASA average threshold levels at 500 through 2 000 Hz for men aged 50—59 years reported by Glorig et al. from the Wisconsin State Fair Hearing Survey are converted to Sivian and White threshold levels, those with »Fair hearing» had a median threshold level of 24 dB with the 75 percentil at 39 dB. The corresponding levels for »Poor hearing» were 49 dB and 65 dB These hearing threshold levels and those of Beasley's grades 1 2 and 3 seem to indicate that the group »mediocre» of the present study comprises the best hearing individuals of Beasley's grade 2 and Glorig et al. s poor hearing group, and the poorest hearing of their grade 1 and fair hearing group, who according to Harford and Barry »can get by' but with noticeable effort» The group poor hearing of the present study corresponds to Beasley s grade 3 and to the poorer hearing half of his grade 2 and to Glorig et al.s poor hearing group

In the present material 244 ears have been examined by clinical conversational voice test using numbers (21—99) in an ordinary consulting room. As shown in Fig 4 the spread of the results is so large that they give no valuable information about the hearing of the individual patient. The median values demonstrate however a steep decline of the hearing distance for conversational voice by hearing threshold level for speech exceeding 40 dB, and coincide with data given by Lidén 1955.

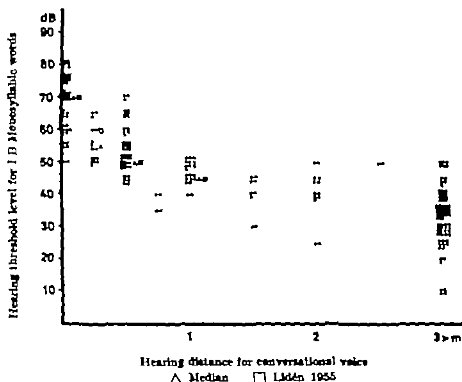


Fig. 4. Hearing distance for conversational voice in relation to hearing threshold level for PB monosyllabic word lists. N=241

The present material of selected patients with predominantly conductive hearing losses has shown good correlation between hearing threshold level for speech and the average hearing threshold level at 500 1 000 and 2 000 Hz.

The relation of subjective appraisal of the hearing to objective assessment is in fair accordance with previous United States reports, and the relation of hearing threshold level for speech to hearing distance for conversational voice coincides with Swedish data.

The result of the present study shows that 35 dB hearing threshold level for speech may be taken as the starting point when one shall decide whether or not the applicant, according to present Norwegian regulations, is entitled to have a hearing aid free of charge provided the has 100 per cent score of PB monosyllabic word lists. In case of discrimination loss the 35 dB hearing threshold level for speech may be replaced by the corresponding Hearing Index 64. Additionally it appears from the study in accordance with the findings of Harford and Barry that the magnitude of the difference between better and worse ear must be taken into consideration to a larger extent than has formerly been done.

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CONDUCTIVE LESIONS IN CHILDREN AND YOUNG ADULTS IN PAST AND PRESENT

PREVALENCE, CAUSES AND TREATMENT [1])

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The frequency of conductive lesions among children in normal school and hearing school has decreased considerably probably because of a better hygiene and more effective treatment. The persistent and severe cases remain, now being referred for treatment in hospital.

Such cases could be divided into two main-groups:

A Cases characterized by *effusion* (secretory otitis) and

B Cases characterized by *destruction*

A Secretory otitis In spite of tubulation and daily suction of persistent tenacious secretion for a very long time stationary hearing has so far been obtained in only one case out of 19 The total protein content was strikingly high in most cases, involving the risk of invasion of fibroblasts.

B Middle ear destruction In nearly one half of the cases the etiology of deafness was revealed by operation presenting congenital malformations, primary cholesteatomas, incus-luxation otosclerosis and chronic adhesive otitis.

Postinfective defect of ossicles and ear drum were more or less mapped before operation.

Postoperative hearing gain, exceeding 20 db (TAA), was obtained in about two third of the patient in this group.

Due to the still more encouraging results of reconstructive middle ear surgery gradually all conductive lesions — not only otosclerosis — have come into the limelight of otology

The scope of this paper is partly to evaluate prevalence and causes of conductive lesions in children in past and present and partly by operation on cases unapproachable to any other treatment to get information on nature and origin of the most severe cases and the possibilities of their treatment

This investigation has been undertaken on Copenhagen school-children composing a unity very suitable for comparative studies of this kind as well as for follow-up examinations.

The hearing of all children in municipal schools in Copenhagen is tested once a year by screening audiometry carried out by the school health nurses.

Children with a loss of hearing exceeding 20 db for two or more frequencies within the field 125—2000 cps or with a loss of 25 db or more for one of the frequencies 4000 or 8000 cps are regarded as suffering from a hearing defect and consequently they are referred to otologist or to the childrens clinic of the State Hearing Centre.

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[1]) This study was supported by the Directorat of the Municipal Hospital Service of Copenhagen.

Frequency of conductive lesions

On the basis of such examinations, carried out by the school health nurses, the otologists and the State Hearing Centre[1]) as well as own examinations, the author has studied the frequency of hearing defects in children and young adults in four municipal schools in Copenhagen comprising altogether 2759 pupils.

HEARING LOSS IN NORMAL SCHOOL

	Total	Conductive lesions	Skt. Hansgades (455 pupils)	Ryesgade (538 pupils)	Vognmandsmarkens (871 pupils)	Bryggervangen (895 pupils)
J. Falbe Hansen 1954	295 (11 6 %)	78 %	16 %	14.5 %	9.5 %	10 %
			15.3 / 14.1		9.8 / 8.5	
G. Everberg 1966	283 (10.4 %)	26.4 %	17.3 % (44.3 % cond.)	10.8 % (18.9 % cond.)	8.4 % (17.8 % cond.)	10.6 % (21 % cond.)
			Socially unfavourable districts		Socially favourable districts	

Fig. 1

A similar investigation was undertaken by Falbe-Hansen in the same four schools in 1954 (comprising then 2550 pupils) The result of the two studies appears from fig 1 It will be seen that on the whole the number of hearing defects is unchanged, but while in 1954 the conductive lesions constituted more than ¾ of all hearing defects, they now amount to no more than ¼

In addition it will be seen that increase in social prosperity has not levelled the different frequency of hearing defects of different social environments, conductive lesions now prevailing, however only in the socially most unfavourable district (Skt. Hansgades School)

NORMAL SCHOOL

Conductive lesions	Falbe Hansen 1954	Everberg 1966
Middle ear catarrh	96 (41 6 %)	57 (75 %)
Middle ear suppuration	28 (12.1 %)	5 (6.6 %)
Sequel after otitis	66 (28.5 %)	7 (9.2 %)
Ear wax or foreign bodies	41 (17.8 %)	6 (7.9 %)
Primary cholesteatom		1 (1.3 %)
Perceptive lesions		
Isolated hearing defects	36	160
Other inner-ear diseases	28	32

Fig. 2.

Nature and distribution of the different conductive lesions in past and present appears from fig 2. The increasing number of isolated, perceptive hearing defects,

[1]) Th ... K C ... F ... M.D St t H aring C tre Copenhagen.

many of which being now recorded in the State Hearing Centre as »blast-lesions» (firework), accounts for the fact that the total amount of hearing defects remains unchanged It will be seen that middle ear catarrh is now — as well as previously — the most common cause of conductive lesions among children in the normal school, being, however more dominant than before. On the other hand middle ear suppuration and sequelae after otitis are met with far more seldom.

HEARING SCHOOL

		Perceptive lesions	Conductive lesions
K. Sorensen	1947 1957	32.8 % 68.5 %	67.2 % 31.5 %
G Everberg	1966	81.9 %	18.1 %

Fig 3

The frequency of conductive lesions in the *hearing school* of Copenhagen has been studied by K. Sorensen in 1947 and 1957 and by the present author in the spring of 1966 (number of pupils 140 and 149 respectively) As will be seen from fig 3 the importance of the conductive lesions is still decreasing

HEARING SCHOOL

Conductive lesions	K. Sorensen		G. Everberg 1966
	1947	1957	(149 pupils)
Sequels of otitis media	48 7 %	47 7 %	33.3 %
Chronic catarrhal otitis	10.5 %	20.5 %	29 6 %
Chronic suppurative otitis	40.8 %	27 0 %	29 6 %
Malformation		4.8 %	7.5 %

Fig 4

Fig 4 shows that although sequelae after otitis still constitute the majority of the conductive lesions, yet this condition is no more as dominating as previously which applies to middle ear suppuration as well. On the other hand adhesive otitis (here synonymous with chronic catarrhal otitis media) seems to be still more frequent.

From the last annual report of the State Hearing Centre of Copenhagen it appears that the chronic adhesive otitis is now the most common conductive lesion, while in 1963 it only ranged as No 3 (Ewertsen)

Cases referred for surgery of deafness

During the last two years 64 children with conductive lesions have been submitted to hearing-improving operation. Two main-groups could be differentiated *A* Middle ear effusions, *B* Middle ear destructions.

A Middle ear effusions

According to the above mentioned statements on the great frequency of adhesive otitis it is interesting to note, that 19 patients, i.e. nearly one third of the patients referred to hospital with longstanding conductive lesions exhibited secretory otitis, — usually considered the forerunner of adhesive otitis. Before admission to hospital the patients had had politzerization, some of them also paracentesis, and adenoidectomy had been done in 13.

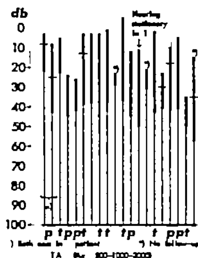


Fig. 5. A cross-line through the column indicates the latest threshold

Fig 5 illustrates the treatment of 19 patients with serous (or secretory) otitis media. In all the patients a transmyringeal soft, short, silicone elastomer tube was inserted after paracentesis and sucking out of secretion, which was in all cases amazingly tenacious. The patient was seen every day as long as secretion was *reproduced. After removal of secretion by suction through the tube, chymotrypsin* and hyaluronidase was instilled into the middle ear through the tube (α-chymotrypsin, 100 Armour units in 2 ml Ringer solution and hyaluronidase, 1000 int. units in 2.5 ml of a physiological sodium chloride solution)

Explorative tympanotomy was done in four cases, preoperative diagnosis being unknown in three.

Evaluating the chance of stationary hearing after this treatment, we must realize that the tube still remains in 7 patients, furthermore that 6 other patients, having had the tube removed, still need politzerization to maintain hearing-gain and finally that the last six patients either have failed to appear for control or have been followed up for less than 3 months after cessation of treatment. Taking these facts into consideration, stationary hearing has been obtained *so far* in only one patient in this series. This seems to be contrary to the optimistic state-

ments of the XV[th] Congress of the Scandinavian Oto-Laryngological Society (1963), but it is in keeping with the assertion of Kersley and Wickham (1966) according to whom the hearing remained stationary in only seven out of 100 cases.

In other words the serous or secretory otitis is characterized by an amazing persistency which may to some extent be due to the fact that viscous secretions are the most difficult ones to cure.

Assuming a correlation between viscosity and protein content of the middle ear secretion as suggested by the somewhat contradicting literature, analysis of protein content has been carried out in 10 out of 19 patients in this series[1]) (One case, No 9 10 was bilateral)

The middle ear secretion, tenacious like glue had to be dissolved in 1N sodium hydroxyde and diluted in physiologic sodiumchloride solution and determination of protein was carried out according to the method of Lowry

By paper electrophoresis and agar electrophoresis it proved that only albumin was present in the secretion. No mucopolysaccharides were found.

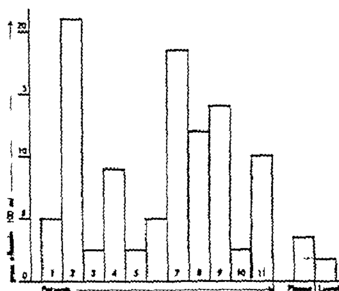


Fig 6.

The concentration of albumin in the different samples varied greatly i.e between 2.5 gram/100 ml and 21 gram/100 ml as appears from fig 6 in which the concentration of albumin in plasma and lymph (of extremities) has been given for the sake of comparison.

Protein content of middle ear fluid in secretory otitis has of late years been thoroughly investigated expecially by scandinavian otologists. The total protein content according to the results of the various investigators, is greatly variable i.e from 1.0 to 16.9 per cent. Serous middle ear fluids have generally been found to have a high total protein content, especially so if the secretory otitis has been of long duration (Robison & Nicholas 1951 Vuori 1959).

[1]) Thanks are d t J. Weis-Fogh M.D wh has undertaken the analysis f all the samples.

According to previous studies all protein fractions occuring in the serum have been encountered in the middle ear fluid in approximately the same proportions as in the serum (Ivstam 1952, Vuori 1959).

Finally it should be mentioned that Zechner et al. (1965) showed the presence of mucopolysaccharides in the middle ear secretion.

Thus it will be seen that the present series differ from other investigations by lack of globulins and mucopolysaccharides, while agreement is found concerning total protein content, being greatly variable with some very high concentrations. In this series, however no correlation was found between protein concentration and duration of the disease.

The low albumin-concentration in some of the cases may be ascribed to technical errors as the tremendously viscous secretions may not in all cases have been collected quantitatively

The high albumin-concentrations, amounting to 5 or 7 times as much as that of plasma, is indicative of an active process of exudation, the source of which being perhaps as pointed out by Kersley and Wickham, the mucous glands of a malfunctioning Eustacian tube.

The presence of highly concentrated protein in the middle ear constitutes a favourable medium of invading fibroblasts, — if not properly treated — converting the disease into chronic adhesive or fibrotic otitis media.

B Middle ear defects

The remaining 2/3 of the patients referred for surgery of deafness exhibited a variety of different defects of the sound conducting apparatus.

From a topographic-diagnostic point of view these patients could be divided into 3 groups, according to our preoperative knowledge of the nature of the lesion (Cf fig. 7).

Group I 19 patients, preoperative diagnosis unknown.
Group II 12 patients, preoperative diagnosis uncertain
Group III 14 patients, preoperative diagnosis evident.

Group I comprises 5 patients with congenital malformation, 6 patients with primary cholesteatoma, 3 patients with luxation of the incudo-stapedial joint 4 patients with otosclerosis and 1 patient with chronic adhesive otitis.

Congenital malformations — (Cf fig 7 According to the diagram the patients are numbered from left to right).

No 1 A girl, aged 8. Explorative tympanotomy revealed a cone-shaped stapes. No hints of oval window present. No attempts of fenestration or mobilization of the ossicular chain was made.

No A girl, aged 8. Facial nerve, partly uncovered, passing through the middle ear No stapes nor oval window present. No attempts were made to restore normal conditions. The patient had also microtia.

No 3 A boy aged 8. Stapes-ankylosis, posterior crus being grossly deformed. Hearing-gain after stapedectomy according to the method of Schuknecht. The patient had also claw-hand.

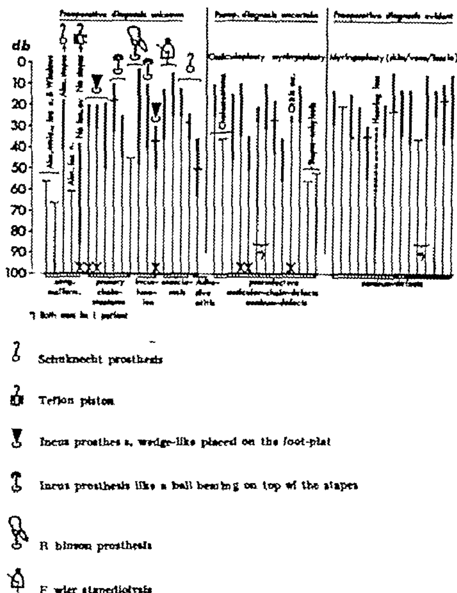


Fig. 7 A cross-line through the column indicates the latest threshold

No 4 A girl, aged 13 Partial right sided facial palsy severe bilateral conducti e lesion. No vestibular function on either side. No semicircular ducts to be seen on tomography Explorative tympanotomy revealed. Stapes absent. Oval window replaced by thick bony masses. Round window replaced by thin fibrous plate Facial nerve ridge passing between these two areas. Incus deformed (long process conical and half the normal length). By drill a fenestration was made on vestibulum, composing an o al window» and a teflon piston was placed in this «window» being hooked around the incus. The hearing was improved to a remarkable extent TAA rising about 50 db

Primary cholesteatoma. — Cholesteatoma behind a normal drum was found in 6 cases. Previous reports are few and far between. In Denmark only 3 cases have been reported during 20 years. Common to all 6 cases were that the cholesteatoma was lying like a pearl in the stapes region, having eroded the long process of incus and/or the superstructures of stapes. The cholesteatomas were hollow bubble-like, collapsing on puncture. When the ossicular-chain defect involved the superstructures of the stapes, it was restored by placing an incus-prosthesis like a wedge, tip standing on the footplate. When only the long process of incus was defect, an incus-prosthesis was placed on the head of the stapes like a ball-bearing In one case presenting complete destruction of the long process of incus and all superstructures a Robinson stainless steel prosthesis was inserted between the neck of the hammer and the foot-plate. 5 of the 6 patients presented hearing-gain to a variable extent.

A detailed publication on primary cholesteatoma will appear later

Luxation of the incudo-stapedial joint was found in 3 patients, one of whom had sustained a severe head injury with haemorrhage from the homolateral ear while only slight head traumas were encountered in two patients, who on the other hand had had otitis and paracentesis many times.

Hearing-gain was obtained by using Robinson-prosthesis (Cf previous patient) or the incus-remnant, placed like a ball-bearing on head of the stapes (Cf above).

Otosclerosis was encountered in 4 patients, aged 9 15 16 and 16 years. Otosclerosis in children is seldom, but has been reported even in a 7 years old child (Shambaugh 1959) Hearing improvement was obtained by the Fowler or Schuknecht method.

Chronic adhesive otitis was found in one patient, a girl, aged 12 years. During the last 6 years she had been controlled in the State Hearing Centre because of right-sided hearing-loss, supposed to be of the miscellaneous type. 2 years before admission to hospital right-sided paracentesis was done with escape of yellow fluid.

Otoscopy revealed nothing particular apart from some fibrosis. Explorative tympanotomy presented numerous adhesions in the middle ear By removing all fibrous adhesions the ossicular-chain was mobilized. Half the hearing-gain was lost within 2 months after which the patient failed to appear for control. — The nearly normal otoscopy is remarkable considering the diagnosis.

Group II comprises 12 patients with postinfective defects of the ear-drum — recognized before operation — and of the ossicular-chain — not recognized before operation, because of which the group has been labelled. »preoperative diagnosis uncertain»

Beside perforation of the ear drum all cases were characterized by interruption of the incudo-stapedial joint affecting the long process of the incus or the super structures of the stapes. Accordingly reconstructive middle ear surgery was carried out in conformity with the above mentioned principles, restoring the ossicular chain by insertion of an incus-prosthesis as an auto- or homotransplantation. The drumperforations were sealed by skin- vein- or — mostly — fascia-graft. The veingraft and especially the fasciagraft was usually placed on the inner side of the perforation.

A dry cholesteatoma was removed in the first two cases, in one of which the graft would not stake due to subsequent infection.

Group III In this group comprising 14 patients, the audiologic diagnosis, i.e. the reason for the hearing loss, was evident.

In all cases a postinfective eardrum perforation was present. In addition some cases presented interruption of the incudo-stapedial joint, which had been recognized already before the operation on otoscopy Ossiculoplasty and myringoplasty was carried out according to the aforementioned principles In order to exclude cholesteatoma (as found in the two cases mentioned above) explorative tympanotomy was undertaken in all cases, even when the ear drum defect seemed to be the only lesion.

It is remarkable that in 19 (Group I) out of the 45 cases, i.e 42.2 per cent the etiology of the hearing loss was revealed only by operation, although in some cases tomography had given some preoperative hints (in fig 7 indicated by X)

Adding the 12 cases with uncertain preoperative diagnosis we find that in more than two third of the cases the true nature of the conductive lesion could be determined only by operation.

Considering the severity of some of the cases (primary cholesteatoma) and the fact that a hearing gain exceeding 20 db (TAA) was obtained in about two third of the patients it seems reasonable to emphasize the importance of doing explorative tympanotomy in any obscure case of conductive lesion.

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AUDITORY ADAPTATION AT THRESHOLD INTENSITIES

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Using the technique of manual adaptation test, recordings of perstimulatory changes at threshold were made during 3-min. stimulation period on 300 patients, suffering mainly of perception deafness. Results are reported of the magnitude of the perstimulatory threshold shift at various frequencies, of the relation of this shift to recruitment phenomenon, and of the frequency of cases with extreme tone decay in various diagnostic groups.

Auditory adaptation at threshold has stimulated as much interest in recent years as did the phenomenon of loudness recruitment 10 to 15 years ago Even the goal is the same, viz. the recognition, that abnormally large adaptation can be associated with a definitely localized lesion in the auditory pathways. The cases showing positive recruitment are, at least at high frequencies, considered to have defective external hair cells. Intact internal hair cells, responding only to loud sounds are considered to be essential for this abnormally rapid growth of loudness at higher levels.

The first audiometric study of auditory adaptation was conducted by Schubert in 1944, and, particularly since 1955, several results — at times contradictory — have been reported. Indeed, although the end-organ was at first considered responsible for adaptation, this view has lately shifted in favor of the auditory nerve

The amount of auditory adaptation is largely dependent upon the testing technique. Two methods are used. one either employes an automatic audiometer with a fixed frequency and the patient himself makes a recording of his threshold during a 3 min. stimulation, or the examiner increases the test intensity by 5 db as soon as the subject reports that he no longer hears the tone in the ear The difference is that in the former technique the tone intensity is alternately increased and decreased, even to total disappearance, while in the latter the intensity change is towards larger values only A third »borderline» method may be used, viz. recording the automatic audiogram with interrupted and continuous tones but owing to continuous change in the test frequency only short-term adaptation can be measured

Both the self-recording and manual technique reveal either slight (5 db) adaptation or none at all in normally hearing subjects during 3 min stimulation; a few listeners, however cannot sustain a tone of the initial intensity In our experience, the normal upper limit can be set at 10 db

In perceptive deafness, the use of the automatic technique generally discloses only moderate amounts of adaptation. Some time ago we examined a series of 279 ears, tested at 353 frequencies and related them to the recruitment function, the measured adaptation loss was found to exceed 10 db at only 41 frequencies, or in

12 per cent. The maximum adaptation in the first series of 56 ears was 28 db in the second of 98 ears 32 db and in the third of 125 ears 70 db The number of ears exhibiting more than 30 db adaptation was only 4 one was a noise sensitive normal ear one a case of acoustic trauma, and the remaining two were both ears of a patient with a tumor affecting the roof of the IVth ventricle.

While the small amplitude of the self-recorded threshold audiogram paralleled the recruitment phenomenon quite closely at the high frequencies (from 3 000 to 6 000 cps) the occurrence of an adaptation exceeding 10 db did not show any distinct relation to either recruiting or nonrecruiting ears in the group of perception deafness. This is clearly apparent from Figure 1 which includes the total material studied by self recording audiometry as related to the recruitment function.

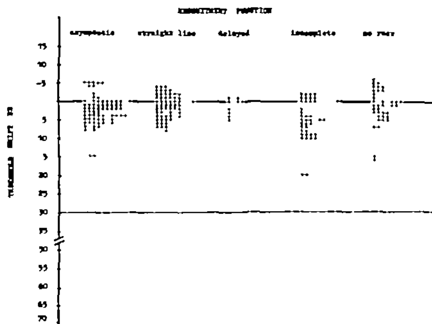


Fig. 1 Auditory adaptation, measured with self recording technique related t recruitment function in 279 ears of perceptiv deafness. The amount of adaptation is similar in all groups.

It was stated earlier that, because of the basic differences in testing procedures, the manual technique of Schubert would probably separate many more cases of increased adaptation than the self-recording technique. Consequently since 1963 we have employed the manual technique as a routine test for measuring auditory adaptation during a 3 min. testing period. The test of course was terminated earlier if the audiometer upper limit did not permit the examiner to follow the receding tone. Indeed, it has become clearly apparent that the amount of adaptation with the manual technique definitely exceeds the figures obtained with the self-record ing audiometer Thus, the present series of 610 ears included 233 ears showing 15—30 db adaptation (38 per cent) The number of ears exhibiting more than 30 db

adaptation was 42 (7 per cent) while the test tone vanished entirely from the test ear in 30 instances (5 per cent)

There is thus no doubt at all that the manual technique is preferable as the routine clinical test for auditory adaptation since it is clearly more sensitive than the self-recording technique. As regards the amount of adaptation, we have divided the patients into four different subgroups: the first includes cases with 0 to 10 db adaptation, the second those with 15 to 30 db the third those exceeding 30 db and the fourth those in which the test tone disappears totally This division differs from Sorensen s in that the limit is set at 30 db in the second group whereas he included in his second group all cases exceeding 10 db but reaching a plateau

Any subdivision is bound to be somewhat arbitrary ours was made on the basis of the finding that in all diagnostic groups there is a large number of cases in which adaptation does not exceed 30 db Vanishing of the test tone again, does not *necessarily mean that the adaptation is extreme but often only that the testing* was done close to the audiometer upper limit because of the high hearing level. On the other hand, the cases showing more than 30 db adaptation in a 3 min. test deviate from normal to such an extent as to necessitate a thorough work-up.

Table 1 shows the clinical classification of all cases tested with the manual technique, and subdivided into the four groups mentioned above. As such, the results apparently do not allow any strict diagnostic labelling of any groups values indicating high adaptation or disappearance of the test tone are found scattered throughout most of the clinical categories.

Figure 2 presents the individual results, using both the selfrecording technique and the manual technique, in one and the same graph in 99 cases of Ménière s disease. The widely differering values of adaptation obtained with these two different techniques are readily seen.

TABLE 1

CLINICAL CLASSIFICATIO CASES TESTED WITH THE MANUAL TECHNIQUE

Diagnosis	Threshold shift (db)				Total
	0–10	15–30	ver 30	tone disappears	
Ménière' disease	21	19	6	8	54
Acoustic trauma	11	11	5	1	28
Noise injury	20	8	2		30
Skull trauma	28	30	7	6	60
Vascular ccident	4	4		4	12
Angiosclerotic degeneration	16	19	3	1	39
Postinfectious deafness	6	3	2	1	12
Vestibular neuronitis	5	6			11
Streptomycin damage	8	7	1	1	17
Hereditary or congenital deafness	21	2		2	25
Presbyacusis	24	17	2	2	45
Nondefined sensoryneural deafness	30	16	3		49
Nondefined vertigo	76	43	2		121
Nerve trunk or infratentorial lesion	8	11	7	4	29
Supratentorial lesion	27	23	3		53
Total	305	233	42	30	610
Per cent	50,0	38,2	6,9	4,9	100

While Ménière s disease represents a clear-cut group of end-organ deafness, the cases in figure 3 represent more or less localized supratentorial or diffuse central lesions. Five tumors, viz. two meningiomas of the frontal lobe and one of the temporal lobe, one falx meningioma of the frontal region and one temporal lobe glioma,

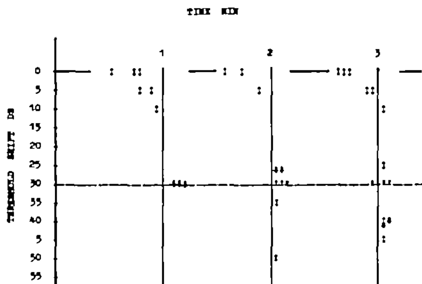


Fig. 2 Auditory adaptation in 99 ears of Ménière disease Results on th left of th vertica lines, are obtained with the self-recording technique, those on the right are with the manual technique. The manual techniqu is clearly the more sensitive one.

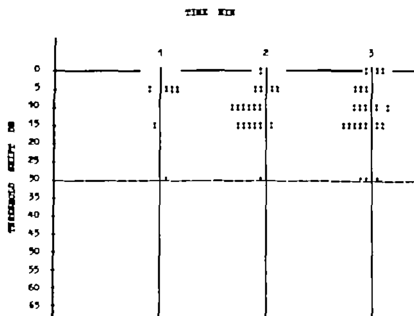


Fig. 3. Auditory adaptation in 35 cases with diffuse supratentorial lesions (left of the vertical lines) and in 23 cases with localized supratentorial lesions (right of the vertical lines) Adaptation exceeds 30 db in 3 ears.

were all verified by operation. In addition there were cases of disseminated sclerosis, cerebral thrombosis, encephalomyelitis, funicular myelosis, meningoencephalitis, epilepsy cerebral infarction, etc. It is seen that adaptation as a rule is not over 30 db but in 3 instances it exceeds this limit. (Cases of left hemiplegia, cerebral atrophy and a probable tumor of the sella turcica region).

A third typical group consists of nerve trunk or infratentorial lesions, all involving either the auditory nerve itself or its pontine pathways. We have included in figure 4 the results of operatively verified cases: one acoustic neurinoma, one metastatic lesion of the cerebellum, 2 papillomatous lesions involving the IVth ventricle, and one parapontine tumor. In addition, we have included one case of cerebellar syndrome and one of compression of the medulla both operated on. There are also 22 cases in which the diagnoses were reached after a thorough neurological work-up including diagnoses of bulbar paralysis, cerebellar syndrome, thrombosis of the vertebral artery etc. Table 2 lists the diagnoses in those cases in which adaptation exceeded 30 db.

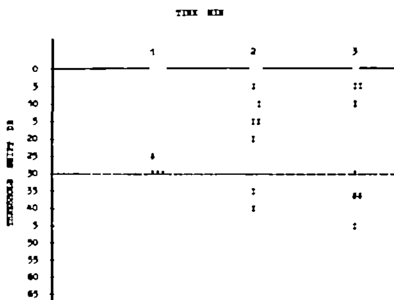


Fig. 4. Auditory adaptation in 29 ears with nerve trunk or infratentorial lesions. Adaptation exceeding 30 db is more frequent and more rapid than in the other groups.

From figures 2 to 4 the conclusion may be drawn that for the adaptation test to be diagnostic, it should give more clear-cut results. In the central lesions, not directly affecting the auditory pathways, the generally low adaptation values are according to expectation. However some of them, and some end-organ lesions like Ménière's disease or acoustic trauma may be associated with a pronounced tone decay and the same applies, but clearly more frequently to infratentorial lesions. It is true that our cases include only one acoustic neuroma. However in Johnson and House's recent series of 53 verified acoustic neuromas there were 9 cases out of 18 in which the tone decay test was normal or showed only slight

TABLE 2

ADAPTATION EXCEEDING 30 DB IN NERVE TRUNK OR INFRATENTORIAL LESIONS

Diagnosis	Ears	Hearing Level (db) Frequencies (cps)					Adaptation (db) at 4 000 cps
		250	500	1 000	2 000	4 000	
Acoustic neurinoma	1	65	70	8[illegible]	95	73	Tone disappears between 250—4 000 cps
Cerebellar metastasis	1	15	15	30	40	100	
Compression of medulla	1	5	0	5	0	40	35
Vascular brain stem lesion	2	5	10	10	0	50	35
		10	0	15	10	20	65
Extrapyramidal syndrome	2	0	5	0	5	10	45
		0	0	5	5	10	45
Progressive spinal atrophy	2	15	10	20	40	65	40
		10	5	15	50	65	Tone disappears
Cerebello-medullar syndrome	1	55	60	65	65	65	

adaptation. This seems definitely to disprove the notion that abnormal adaptation is pathognomonic of retrocochlear nerve lesions.

We have stressed earlier that abnormal adaptation, showing more than 30 db loss during 3 min. stimulation, or total disappearance of the test tone, should arouse the suspicion of acoustic neuroma, but that a complete neurological examination is needed to arrive at this diagnosis. *Furthermore it is obvious that a number of* cases of acoustic tumor show only slight adaptation. We are still at a loss to under stand clearly what happens electrophysiologically and where, in cases of pronounced adaptation. None of the studies measuring the cochlear potentials or auditory nerve responses after prolonged stimulation or after slight damage to the nerve have shown more than very minor changes, not comparable to clinical findings. Much additional work will be needed before the exact nature of the adaptation phenomenon will be fully understood at that time, definite clinical conclusions will probably also be possible.

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CONDUCTIVE RECRUITMENT

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Twenty-four cases f unilateral pure conductive loss due to fixation of the ossicular chain have been examined by objective recruitment test (stapedius reflex measurement). In all of them the stapedius reflex was recorded on acoustic timulation f the affected ear in spit of the absence f conditions for achieving dequate stimulatio owing t the conductiv loss. Th distance between the hearing and reflex thresholds diminishes with the severity of the hearing loss. Such reduction is usually considered t indicat recruitment.

In a binaural balance test similar low-grade but definite recruitment was found. That th phenomenon is dependent on the conduction defect is confirmed by comparati measurements before and after operation.

In 6 cases f interruption or dislocation in the ossicular chain the degree of recruitment was considerably less marked if not entirely bsent and this applies also t a conductive loss produced experimentally by plugging the a ditory canal.

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DISCUSSION

T Palva, Oulu, Finland, to Barr

Th appearance of incomplete loudness recruitment in conductive deafness is very interesting d I have myself reported on some such cases ten years ago. As otosclerosis particularly seems t be associated with this phenomenon, one reason could be in an altered sensitivity of the hair cells due to different composition of the cochlear fluids as compared to normal. At least in the perilymph th concentration of alcaline phosphatase and of total protein seem to be considerably higher than the normal values. However as postoperatively there is no difference between the ears, the reason can hardly be du to this factor

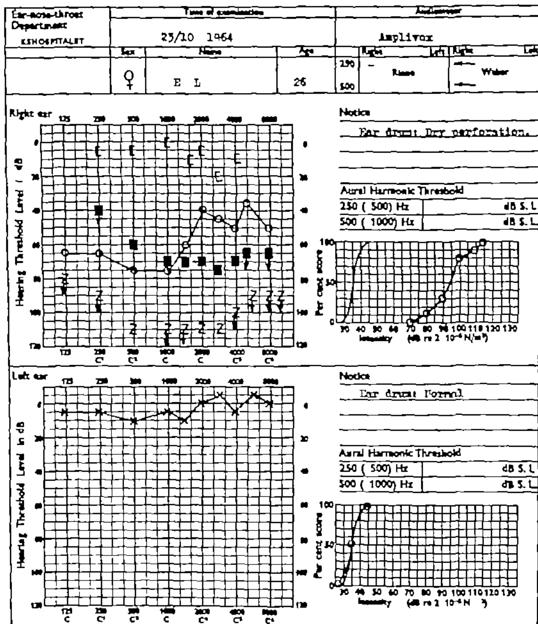
There is another more real explanation, and this is possible over hearing t higher levels. Let us assume that the difference between the ears t threshold is 60 db, proper masking being employed in the nontest ear The interaural insulation in Fowler' test without no masking t high levels, may not be more than 35—40 db, and one would get a loudness recruitment of 20—25 db

In tosclerosis, different degrees of fixation also alters the conductivity variously t various frequencies. I wonder if Dr Barr has observed any clear frequency differences also t suprathreshold levels between low tones and high tones, d whether he has measured the growth f loudness also using white noise as th test stimulus.

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At Rikshospital t in Oslo patients with unilateral pure conductive hearing loss have been examined by recruitment test ad modum Metz (stapedius reflex measurement) and by Fowl r's binaural balance test. Our observations are in agreement with those described by Anderson and Barr



Z Threshold lev l for the acoustically licited tapedius reflex air condu ti

■ – bon

Additionally it was observed that th threshold level for the acoustically licited stapedius reflex was much lower for bone conduction than for air cond ction timuli (see fig 1). In normal ears the stapedius reflex threshold level for air and for bon conduction stimuli is about the same.

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SUDDEN DEAFNESS WITH SPECIAL REFERENCE TO ANTICOAGULANT TREATMENT

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I 1961—1965, total of 102 cases of sudden deafness with no symptoms other than those emanating from the tatoacoustic nerve were examined and treated t the Otolaryngological Hospital of th University of Helsinki. Fifty two patients were treated with Heparin, all of them reporting for treatment within 3 day of the loss of hearing. The remaining 50 patients were managed without Heparin and came for treatment 4 days—4 weeks after the onset of the deafness. The latter material, consequently cannot be used t control the efficaciousness of Heparin therapy

The verage improvement in hearing during the mean observation period f 189 days was 29 dB for the Heparin-treated cases. The hearing threshold was 30 dB at the most (NPL-standard) at follow-up total of 19 patients and in 13 of them t the most 15 dB. The corresponding results for the non-Heparin group were 4 and 2. It was necessary in 2 cases to discontinue the Heparin therapy for reasons obviously due to the drug. Fifty seven patient had subjective vertigo in connection with th loss f hearing. Unilateral disturbance of vestibular function was established initially in 52 patients in the ear that sustained the acute loss of hearing.

Sudden deafness (Plötzlicher Hörsturz) is a disease every otologist is familiar with, and numerous studies on the subject have been published. The term sudden deafness is generally used in cases when an otherwise healthy person suffers an acute partial or complete loss of hearing in one ear and there are no other symptoms but those emanating from the stato-acoustic nerve. Although we have a fairly accurate knowledge of the various reasons which may cause a sudden loss of hearing it is often difficult, and can even be impossible in individual cases, to discover the fundamental cause of the deafness. Obviously a variety of factors may produce sudden deafness. Circulatory disturbances and viral infections are generally held to be the most important reasons.

Ganz (1965) regards circulatory disturbances as the commonest cause of sudden loss of hearing and distributes them into two groups: I Organic reasons which are thrombosis, embolism, arteriosclerosis and endarteritis obliterans of the auditory artery and hemorrhage into the labyrinth. II Functional causes arising from diathesis of the vessels of the internal ear on a vasoneurotic basis, which in turn leads to hydrops. In 19 of the 22 cases in this author s material the cause was a circulatory disturbance of the inner ear The causes of sudden deafness are divided by Dietzel (1963) into three main groups. Neuritis n.cochlearis, obliteration of the labyrinthine vessels, and neurovegetative, functional circulatory disturbances of the labyrinth Also Steinmann (1965) regards circulatory disturbances of the internal ear as an important cause of sudden deafness, but he admits also the great etiologic significance of viral infection. Infection by a neurotropic virus is considered to be the most important cause of this disease by van Dishoeck (1957),

while Lehnhardt (1958) holds that a local allergic toxic condition is involved Many other workers, Bocca and Giordano (1956), Rasmussen (1949), Lindsay and Zuidema (1950), are of the opinion that viral infection is the most important cause of sudden deafness. On the other hand, Fowler (1950) attributes it to the sludging phenomenons of red blood cells which is furthered by stress, intoxication noise and pathologic loading of the cervical spine.

It is obvious that circulatory disturbances of the inner ear are not the only cause of sudden deafness, for those affected include a considerable number of young persons with no signs of disturbance in the circulatory system A large proportion of the 16 cases reported by Zuidema were young subjects. Van Dishoeck and Bierman published 100 cases, but the majority of them were old or middle-aged.

Some patients who suffer a sudden loss of hearing also have vestibular symptoms. The lower incidence of vestibular symptoms is attributed by Perlman, Kimura and Fernandez to the fact that lack of oxygen does not damage the vestibule as readily as the cochlea. According to Dietzel, vestibular symptoms impair the prognosis of hearing

As there are many reasons leading to sudden deafness and since it is not always possible to establish the etiology the threrapy varies fairly greatly from hospital to hospital. In fact, Ganz recommends that the patient be admitted to hospital and uses chiefly stellate blocks and medicaments such as Hydergin Complamin and Rovigon A case was reported by Harbert and Young (1964) in which the patient was given procaine intravenously resulting in the return of normal hearing in 4 months. Besides loss of hearing, however this patient also had facial paralysis, vertigo and double vision which like the deafness, had appeared after an infection. Jakobi and Skurczynski (1964), who attributed sudden deafness to labyrinthine hydrops, treated 41 cases by vestibulotomy They achieved a definite improvement in hearing in 19 cases, normal hearing was restored to 9 patients All the patients whose hearing returned to normal were operated on within 4 days of the loss of hearing, and none of them had vestibular symptoms. Vestibulotomy is beneficial only in a recent case in which other threapy also frequently gives a good result.

Two cases treated by Heparin were reported by Covas (1964) One was a man of 44 who was treated within 22 hours of the onset of the deafness. He was given 1 c.cm (5 000 IE) of Heparin every 6th hour for 48 hours and in addition 1 Sinthrom tablet (2 mg) twice daily for 9 days. His hearing was normalised in 9 days. The other patient was a woman aged 35 who was admitted on the 4th day after the loss of hearing The treatment was the same as for the other patient, but it was continued for 14 days. Her hearing began to return on the 7th day and rose from the level of 80 dB to 20 dB in the low tones, recovery was less complete in the high notes.

Purpose of the Investigation

The purpose of the present work was to ascertain the extent to which vestibular symptoms accompany sudden deafness and to examine the usefulness of anticoagulation therapy when it is not possible to define the cause of the hearing loss with certainty

Investigation material

A total of 114 patients with sudden unilateral deafness were treated at the Otorhinolaryngological Hospital of the University of Helsinki in 1961—1965. Twelve of them were either cases with symptoms deriving from cerebral nerves other than the stato-acoustic nerve or were patients who had sought treatment more than a month after the loss of hearing. These cases were not included in the material. The remaining material, 102 patients, can be divided into two groups: I. Persons who sought treatment within 3 days of the onset of deafness and were given Heparin. They constitute the main part of the present study. II. Persons who had sought treatment over 3 days but at the latest within a month after the loss of hearing and were not given Heparin. There was no sexual bias in the series: 48 were women and 54 men. The age distribution is given in Table 1.

TABLE 1

AGE DISTRIBUTION OF THE MATERIAL

Age	Number of cases	Age	Number of cases
Under 21 years	4	41—50 years	25
21—30	20	51—60	29
31—40	18	Over 60	6

Nearly a fourth of them were no more than 30 years old, and there were only 6 elderly over 60.

Method of investigation

The preliminary data on each patient was as detailed as possible. A particular effort was made to discover any diseases that might have preceded the loss of hearing and the conditions in which the loss was sustained. The occurrence of vertigo and the order of appearance of the symptoms (tinnitus, loss of hearing, vertigo) were recorded as carefully as possible. Clinical examination of the ears, nose, pharynx, epipharynx and larynx was then performed. Audiologic examination. All the patients were given pure tone audiometry and also speech audiometry in which both the speech threshold and maximal discrimination score were examined. Recruitment was studied by Fowler's method when possible on the basis of hearing in the poorer ear. Special tests were performed on some of the patients, e.g. adaptation determinations. Vestibular examination. Calorisation was performed on all the patients by the method of Dix Hallpike in addition to the observation of spontaneous nystagmus. Calorisation was performed with water of 30 and 44 but not colder than 30. Both spontaneous nystagmus and caloric nystagmus were registered electronystagmographically. The same examinations as were made on admission to hospital were repeated at the follow-up.

Therapy

The quantity of Heparin administered in the first 24 hours was 6—8 ccm, depending on the person, given in 3 doses. The subsequent dosage depended on the pa-

tient s reaction and was sometimes smaller Heparin was usually administered 8—12 days, sometimes even for 14 days. In addition multivitamin preparations were given and drugs to stimulate the circulation (Complamin Ilidar Thinicol) chiefly as a continuation to Heparin therapy The last-mentioned drugs were given as the principal treatment to nearly all the patients who had come for treatment within 3 days of the onset of deafness whether or not the loss of hearing was found to have been caused by a circulatory disturbance. In some recent cases Heparin therapy was either regarded as contraindicated or the cause of the hearing loss was such that Heparing would have given no benefit.

Results

1 *Anamnestic data* All the patients had previously had normal hearing in the ear which suddenly went deaf. The hearing was impaired in the contralateral ear of 9 patients: It had been caused in 3 patients by sudden deafness, in 2 by chronic otitis and 4 by sequela of otitis. All 102 patients said that they felt completely healthy immediately before the sudden onset of the hearing defect. Sixty five patients reported that the loss of hearing had occurred very rapidly sometimes in a few minutes, whereas 22 stated that it happened within a few hours. Fifteen patients reported that the onset of the hearing defect occurred at night during sleep Three patients developed the hearing defect either in a hot sauna bath or immediately after it, 2 patients had stopped intensely noisy work a couple of hours before the onset and one patient had been awake the entire previous night driving a car Forty five persons suffered no vertigo in connection with the hearing loss. Fifty seven had a history of vertigo 10 patients had only slight vertigo which did not interfere with their movements to any major extent, 32 found it difficult to move about because of vertigo and 15 had such severe vertigo that they were unable to walk without support. Tinnitus was absent in only 6 out of 102 cases, and 44 patients had vomiting or nausea at the outset. Hardness of hearing was the first symptom in 46 cases, tinnitus in 45 and vertigo in 11 cases.

2. *Start of therapy* Fifty six patients came for treatment within 3 days of the onset of deafness, 31 of them within 24 hours. Twenty patients sought treatment within 4—7 days of the complaint, 24 in the second or third week and 2 not until the impairment had persisted for almost 4 weeks. A total of 38 cases were treated at the out patient department, and 64 patients were hospitalised, most of them fresh cases. The average treatment time in hospital was 12 days.

3 *Otological examination* None of the patients had a purulent discharge from the ear which had suffered the hearing loss. One had a dry perforation in the tympanic membrane and 2 had secondary membrane. Nothing pathologic was established otoscopically in 99 cases.

4 *Audiologic examination* The following data concerning hearing tests and vestibular examinations apply only to the ear affected with sudden deafness. The hearing threshold on starting therapy can be seen from Table 2.

It was possible in the speech audiometry examination to determine the speech reception threshold of 50 persons, but in 52 cases 50 per cent intelligibility was not achieved even at maximum intensity

TABLE 2

HEARING THRESHOLD DETERMINED BY PURE TONE AUDIOMETRY MEAN O THE FREQUENCIES 500 – 1000 – 2000 c. .s.

Hearing threshold	Total material 102 cases	Cases treated with Heparin, 52 cases
Ear deaf	18	9
Hearing only in the range 125 – 500 c.p.s.	5	—
Over 90 dB	21	9
61 – 90 dB	36	22
31 – 60 dB	22	12
Total	102	52

Nine of the 52 patients gi en *Heparin therapy* were cases in which the speech reception threshold was impossible to measure at the time therapy was instituted. The mean was 71 dB for the remaining 43 patients. The follow-up examination was performed 2 months—1 1/2 years (average 139 days) after the beginning of hardness of hearing, and the pure tone threshold was then as follows.

TABLE 3

THE PURE TONE THRESHOLD ATIENTS IVEN HEPARIN THERAPY 139 DAYS AFTER THE ONSET F THE HEARIN DEFECT

Hearing threshold	Number	Hearing threshold	Number
10 dB under	8	61 – 70 dB	5
11 – 20 dB	8	71 – 80 dB	3
21 – 30 dB	3	81 – 90 dB	5
31 – 40 dB	5	91 – 100 dB	2
41 – 50 dB	5	Not measurable	3
51 – 60 dB	5		

The therapeutic result was thus fairly good in some of the cases: The hearing threshold was 15 dB or better in 13 cases, exactly one-fourth of the total, and if 30 dB is regarded as the limit of socially adequate hearing, 19 of the patients came in this category. Six of the 9 patients whose threshold was impossible to measure initially showed a notable improvement in hearing. At the follow-up, one of these had a pure tone threshold of 22 dB and another of 31 dB. The mean hearing threshold which was 71 dB initially was 42 dB after an average of 5 months; thus, the improvement was 29 dB. Fifty per cent intelligibility was achieved in speech audiometry by only 24 of the patients given heparin, but 5 months later the figure was 41. An average improvement by 22 dB occurred during the observation period in the cases in which it was possible to determine the speech threshold both on starting therapy and at the follow-up examination.

5. Vestibular examination. Eighteen patients had spontaneous nystagmus on starting therapy. At the follow-up examination which was performed an a erage of of 139 days later spontaneous nystagmus occurred only in one patient, and in this case the follow up was 2 months after the onset of the hearing loss. The vestibular function initially and at follow-up can be seen in Table 4.

In 2 Fällen musste die Behandlung mit Heparin unterbrochen werden aus Gründen die wahrscheinlich auf das Heparin beruhte. Mit der eingetretenen Taubheit erfuhren 57 Patienten subjetives Schwindelgefühl. Eine unilaterale Vestibularisstörung auf der Seite der Taubheit wurde bei 52 Patienten festgestellt

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DISCUSSION

Everberg to Lumio and Aho

Th. A. Biermann s dissertation from Leyden (1957): »Sudden Perceptive Deafness should be drawn attention to here, all the more so as it is rarely quoted, — strange to say as it represents one of the most objective attempts to study the etiology of sudden deafness.

Biermann studied 110 cases of sudden deafness. Benign serous meningitis was found in 14 cases. In 23 cases positive serologic reactions were found and among them in not less than 14 cases for the mumps virus. In 7 cases positive reactions were found for the enteric group: i. 5 for Columbia S.K. and 2 for the Coxsacki group. For the influenza group 7 positive reactions were found. Previous investigators have not sufficiently distinguished between the etiology and pathogenesis of acute perceptive deafness. As a result, circulatory disturbances and labyrinthine hydrops have often been stipulated as causes while it must be assumed that a deeper cause must underly these pathogenetically important mechanisms. Thus oedema and abnormalities in the blood vessels will always be found together with infection. (Biermann).

Furthermore attention should be drawn to the possibility of familiar predisposition. In 1957 Everberg (Acta Otolaryngol (Stockholm) 47 303) referred to a family three members of which were struck by sudden deafness, and in 1960 (Ann Otolaryng 69 711) to two other families, different members of which presented congenital or sudden deafness. This is by analogy with the findings made by Lindenow (1915) and Kristensen (1948) in the case of sporadic, recessive deaf-mutism.

Serologic and genetic studies carried out on large series of sudden deafness are likely to widen our etiologic knowledge of this peculiar symptom.

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AUDIO-VISUAL REFLEX

DETERMINATION OF THE AUDIO-VISUAL REFLEX IN DIRECTIONAL HEARING BY EMPLOYMENT OF ELECTRONYSTAGMOGRAPHY

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The audio-visual reflex has been registered by means of DC-electronystagmograph in series of 10 normal-hearing adults. The acoustic stimulus is an octave filtered white noise band around 1 000 cps with an intensity of 60 db emitted at random from 7 loud-speakers, placed in a half-circle with an interval of 20 degrees, the maximal deviation from azimuth being ± 60 degrees. The deflections of the eyes in the dark towards the sound are compared to the calibration curve, where light signals replace the loud-speakers. The reliability of this last method has been determined to be ± 2.7 while the standard deviation of the lateralization of sound was found to have mean value of ± 8.3° increasing in the most lateral positions. Experiments with 2 ear-level hearing aids gave results with no statistical difference from experiments with the unaided ears, while one pocket hearing aid connected to both ears through a Y-cord gave no lateralization at all.

The ability of localization in primite life is of paramount importance for the survival of the individual. This function is dependent on two normally-functioning ears, the primary role of which is to direct the eyes towards the source of sound in order to identify its nature. Directional hearing of *lateralization* is the ability to judge only the direction of a sound source while *localization* also includes evaluation of the distance.

Lateralization has been examined either by means of head-phones or in free field examination using pure tones or complex sounds. The ability to lateralize sounds depends on differences in time of arrival and intensity differences between the stimuli of the two ears. Headphones offer good possibilities for experiment with these factors, but in this report we shall confine ourselves to free field examination with a complex sound, as this is more physiological (natural) and necessary for the clinical evaluation of the effect of two hearing aids. Wilska (1938) Jongkees and Groen (1946) and many others have found that it is easier to determine the direction of a complex sound than that of a pure tone.

Nordlund (1963) used an anechoic chamber where a loudspeaker could be moved on a horizontal semi-circle behind a cloth at a distance of 1 meter from the head of the subject. On the cloth was painted a scale graduating from 0—140° When the loudspeaker was placed in various positions, the subject had to indicate the corresponding scale mark. The difference between the estimated and the true posi-

tion of the loudspeaker in relation to the scale gave the angle of error and thus a measure of the subject s ability to localize a sound source. A series of tests were carried out on 8 normal-hearing subjects with their heads set in a fixed position, and the loudspeaker was moved in steps chosen at random between the limits of —30 and +30 on either side of the median plan (azimuth). The standard deviation when localizing the position of the loudspeaker was found to be +7,2° for a pure tone of about 1 000 cps while the lateralization of a low pass filtered white noise was more precise with a standard deviation of only +2,3

Jongkees and de Veer (1957) have described a way of examining directional hearing by means of a little loudspeaker placed at a distance of 50 cm from the subject s head. The loudspeaker can be moved +90° from azimuth, and then the subject has to point out with closed eyes the position of the loudspeaker We copied this method at the State Hearing Centre of Copenhagen, using a small loudspeaker giving a maximum output not exceeding 60 db for experiments with speech lateralization (Funch 1962). Given the short distance and the little loudspeaker we found it unnecessary to have an anechoic chamber at our disposal, because the effect of reverberation was negligible

In the present study we have tried out a new method of studying directional hearing by registering the turning of the eyes in the dark towards the sound source Furthermore, we have examined the effect of two ear-level hearing aids, compared with one pocket hearing aid, which through a Y-cord transmitted stimuli to both ears simultaneously

It would be well to recall briefly the anatomical path-ways leading from the ear t the brain (Jungert 1958). The first neurons having their trofic centres in the spiral ganglion end in the cochlear nucleus with its dorsal and ventral parts. The second neurons having their trofic centres in nucleus lemnisci lateralis and ventralis pass crossed and uncrossed to the inferior colliculus. The crossed path-ways from the dorsal part of the cochlear nucleus are seen in striae medullares acusticae while the crossed path-ways from the ventral part of the cochlear nucleus form the corpus trapezoideum. In corpus trapezoideum groups of cells are found — among those the so-called nucleus olivaris superior and nucleus olivaris accessorius Galambos (1957) discovered cells in the accessory nucleus of the cat, which showed exquisite physiological sensitivity to intra-aural time difference A study of one of these cells shows the cell to re-act when both ears are stimulated exactly together but t become wholly silent when the right ear stimulus precedes the left one by the exceedingly short time interval of half a milli-second. This experiment proves the importance of the role of nucleus olivaris accessorius in lateralization.

From the nucleus olivaris superior some fibres pass to nucleus nervi abducentis, to nucleus nervi trochlearis, to nucleus nervi occulomotorius, nucleus nervi accessorius and nucleus nervi facialis. Through these path-ways the quick reflexive turning of head and eyes upon the occurrence of a sudden loud sound represents one form of binaural interaction that can take place in the absence of anything central to the medulla. Deatherage (1966) writes. In the psychophysics of hearing on the other hand, complex judgements of centre left and right without a doubt deeply involve the central neural system. Binaural interactions may occur with or without sconsciousness.

It is a well-known fact from electro-nystagmografic examinations, e.g Henriksson (1956) that the cornea-retina potential indicates variations of the axis of the eyes, and by means of a D C. amplifier it is possible to demonstrate clearly alterations in the electric field in the surroundings of the eyes parallel to deviation of the axis of the eyes.

Present Investigation

Apparatus

On a horizontal half-circle with a radius of 60 cm (2 ft) 7 hearing aid earphones were placed in little poles with an interval of 20° from +60 till —60° Above each ear phone a lamp was placed The lights could be lit, and an octave band filtered white noise with centre frequency 1 000 cps. could at random be switched to any of the little poles numbered from 1—7 as seen on Fig. 1



Fig 1 Equipment for registration of the audio-visual reflex.

The subject's head was placed in a special frame ordinarily used by oftalmologists for the fixation of the head and chin. Three electrodes were fixed to the skin around the eyes (to the outer canthi) and connected to a DC-amplifier coupled to a mingograph. thus recording the horizontal movements of the eyes.

Method

The purpose of this investigation is to try out a new way not hitherto described, of lateralization by electro-nystagmografic registration of the turning of the eyes towards a sound. To begin with, a calibration has to be done by visual fixation of lamps.

The test-subjects were instructed to look spontaneously at the lamps as they were lit in an arbitary sequence and in this way the horizontal deviation of the

eyes on the mingograph was counted in millimeters. The correlation between angular deviation and curve deflection was not linear but it was found that the deflection was proportional to the sinus of the angular deviation. According to the amplification it was necessary to make up a correlation curve for each of the ten test subjects.

After the calibration with the lamps had been fulfilled the patients were asked in the darkness to direct their eyes spontaneously towards each little ear-phone as soon as it transmitted a sound. The experiment had to take place after 5 minutes in absolute darkness to allow for a stabilization of the cornea retina potential. Of course the darkness also was necessary because the subject would otherwise choose between one of the seven possible positions, and we would not get any estimation of the exactness of lateralization.

The first part of the experiment with lighting of the 7 lamps was performed five times on each subject and the deflection measured in millimeters was averaged according to the various positions of the lamps. The reliability of the method is calculated from the standard deviation measured in degrees for the single individual and for all the ten of them, see Fig. 2.

Position of lamp	− 60	− 40	− 20	0	+ 20	+ 40	+ 60
S.D. in degrees	± 3.3	± 2.7	± 1.6	± 0.8	± 1.6	± 3.3	± 5.5

Fig. 2. gives th mean error of the observations with the axis of the eyes in the various positions.

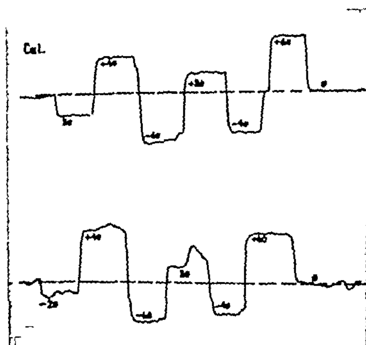


Fig. 3. show the registered calibration curve for the lamps (up) and the hearing lateralization curv (down). In the lower curve it is seen in the middle (+ 20 how the spontaneous lateralization is corrected by th consciousness.

The second part of the experiment concerned lateralization in the darkness by means of band noise around 1 000 cps and was performed 3 times through all the 7 ear-phones at random. Finally the equipment was calibrated again by means of the lamps, see Fig 3.

Material

Ten normal-hearing persons aged from 25—53 years were examined following the procedure indicated above The investigation falls in three groups:

1) Lateralization without hearing aids
2) Lateralization by means of two ear-level hearing aids connected to the ears of the subject by means of individually well-fitting ear moulds.
3) Lateralization by means of a pocket hearing aid placed on the upper part of the chest in the midline

Results

ad 1 Lateralization without hearing aids. Fig 4 illustrates the average values of the initial spontaneous deflection indicated in degrees for all the ten subjects together with the S.D on all the readings. The ordinate indicates the distance of the found source from azimuth measured in degrees, and the abscissa gives the registered deviations of the eyes. It is obvious that lateralization is less exact in the lateral positions, and the subjects have a tendency to indicate a more medial position of the sound source than is actually the case

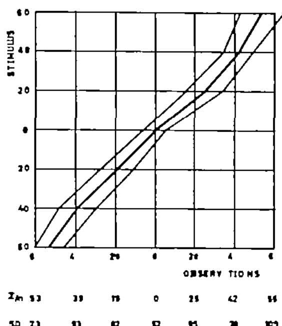
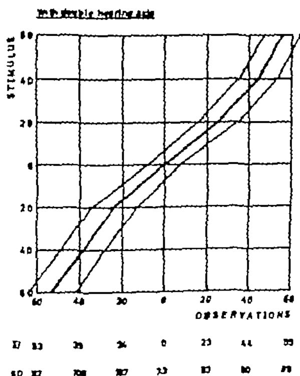


Fig. 4. See text for explanation.

ad 2 Lateralization by means of two hearing aids. The subjects were allowed to adjust the *ear-level hearing aids in front of the azimuth ear-phone, until they* had a feeling of mid-line hearing With the two ear-level aids, the lateralization was statistically as exact as the lateralization without hearing aids, i e. no significant difference with or without hearing aids, see Fig 5



ad 3 With one pocket hearing aid connected to both ears, the sound source would nearly always be localized in front of the subject — no matter which ear phone was emitting sound in the various positions.

Comments

It has been demonstrated that it is possible to use the electro-nystagmografic registration of the turning of the eyes towards the sound source in lateralization examinations. The mean value of the standard deviations is ± 8 3 *Nordlund* found a standard deviation of $\pm$ 7.2° for a pure tone of 1 000 cps, and only $\pm$ 2.5 for the low pass filtered white noise. Nordlund s experiments in an anechoic chamber are not comparable with ours, as we use an octave filtered white noise around 1 000 cps and a quite different equipment.

We know that our apparatus may be a little complicated but it is an advantage that the experiments can be performed without an anechoic chamber and moreover our method gives *unreflected spontaneous localization in darkness for the pure* audio-visual reflex without consciousness.

Two ear-level hearing aids can be adjusted so that the lateralization by means of these is as exact as that of the normal ears.

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ON THE CONTINUOUS CONTROL OF THE MIDDLE EAR MUSCLE ACTIVITY IN CAT

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Middle ear muscle activity in response to clicks was quantitatively evaluated by electronic integration of electromyography. An integrator capable of dealing linearly with successive short bursts of electromyographic activity was developed. If the same click was applied repeatedly the EMG response varied and for quantitative evaluation it was necessary to establish average responses using an on-line average computor on 25—30 responses obtained at an interval of 10 seconds. Interactions between two clicks applied with intervals varying from 5 msec to 500 msec were studied using this technique. These studies indicate that.

A) Interaction between successive stimuli occurs both in the form of facilitation and inhibition.

B) Facilitation and inhibition do not run parallel in the two middle ear muscles, indicating that these muscles are not true synergists.

C) Small differences in sound pressure (2 dB at a level of 80 dB HL) are capable of changing the middle ear muscle response indicating that the middle ear muscles are part of a fine mechanism involved in acoustic perception.

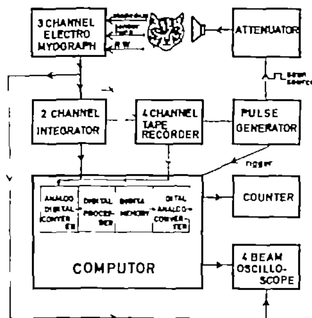
D) Interaction patterns depend on the cat's alertness, expectancy and experience with the stimuli.

E) Both response type and interaction pattern are completely and unpredictably changed by decerebration, indicating that further progress can be made only with intact animals.

The integrated electrical activity of the electromyogram is proportional to the force of a muscle contraction (Bigland and Lippold, 1954, Rosenfalch 1959). Middle ear muscle activity in response to clicks was quantitatively evaluated by electronic integration of electromyography recorded via chronically implanted bipolar stainless steel electrodes. An integrator capable of dealing linearly with succesive short bursts of electromyographic acitivity was developed (Salomon 1966) since click responses in the middle ear muscles consists of this type of activity (Salomon & Starr 1965). If the same click was applied repeatedly the EMG response varied and for quantitative evaluation it was necessary to establish average responses using an on-line average computor on 25—30 responses obtained at an interval of 10 seconds. Schema of equipment see Fig 1

Interaction between two clicks of equal loudness applied with intervals varying from 5 msec to 500 msec were studied. At moderate click levels (75 dB) both muscles showed inhibition of the test response when this followed shortly after the conditioning click and facilitation when the interval was bigger The facilitation lasted up to 500 msec.

This work was conducted whilst the author was Senior Visiting F llow at the Institute of Laryngology and Otology working on a Science Research Council's grant.



SCHEMA OF EQUIPMENT

Fig. 1

Inhibition and facilitation do not run parallelly in the two middle ear muscles.

The period of inhibition in the Tensor Tympany lasted about 25 msec, while the inhibition in Stapedius lasted much longer In both muscles the inhibition diminished the test response to 50 of the conditioning response but whereas the facilitation in Tensor Tympany amounted to 200 %, the facilitation in Stapedius was only slight, about 25 %.

With increasing click intensities the duration of the inhibition became shorter in both muscles and in Stapedius the degree of inhibition was reduced. The values for interaction were depending on small changes in click intensities and were still provable for 2 dB changes. The interaction patterns were also depending on the cat's alertness, expectancy and experience with the stimuly

After intercollicular decerebration both muscles showed but a long up to 500 msec lasting marked inhibition, fundamentally different from the response pattern in the intact animal.

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SIZE AND DURATION OF ACOUSTICALLY ELICITED IMPEDANCE CHANGES IN MAN

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The results of th present investigations show

1) The threshold for the acoustically elicited impedance changes is lower for white noise and low frequency stimuli than for high frequency stimuli.
2) The size f the acoustically elicited impedance changes is larger for low frequency stimuli than for high frequency stimuli of the same intensity above the impedance threshold.
3) The increase of impedance change as a function of increased stimulus intensity is faster for low frequency stimuli than for high frequency stimuli.
4) The duration of the acoustically elicited impedance changes is longer for continuous low frequency stimulation of the same intensity above the impedance threshold.
5) As far as the impedance change of the middle ear is considered a protective mechanism for noise induced hearing loss, our results indicat that the inner ear in this respect is better protected when exposed to low frequency sound than t high frequency sound.

The object of the investigation was to study the threshold, size and duration of the acoustically elicited impedance changes of the middle ear in relation to the frequency and intensity of the stimulus (pure tones, white noise, octave band of white noise)

Material and methods

The investigation was carried out in a group of men and women aged 16 to 36 years. All the test subjects had normal hearing for the frequencies included in the investigation. None f them showed signs of disease or sequelae after disease that might influence the investigation.

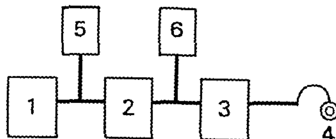


Figure 1 Block diagram of the apparatus to produce and control the stimulus. 1 Beat frequency oscillator 2 Electronic switch, 3. Attenuator 4 Earphone, 5 Electronic counter 6: Tube volt meter

The stimulus tone was applied to one ear The tone was on for about 1.8 secs. and off for about 3.4 secs. The rise and fall time was chosen so as t just avoid hearing a sclick (20 msecs.).

The sound source was Beat Frequency Oscillator (Radiometer HO12dW3), the frequency of which was controlled on an Electronic Counter (Van der Heem). Th tone was interrupted by means of an Electronic Switch (Grason-Stadler Model 829-S-4).

The voltage level and the rythm f the signal were checked on a Tube Volt Meter (Brüel and Kjær 2401) across power Attenuator (Grason-Stadler Model 602) which controlled the sound level of the earphone (Permoflux PDR 8) Fig. 1. The sound level in the earphone was checked on 6 cm³ coupler (IEC-standard) and the ttenuator settings calibrated according to these data.

Th investigation tarted using an intensity of the stimulus tone of about 4—6 dB below the simpedance threshold i.e. the level of a pure tone stimuli to one ear (dB re. ISO standard hearing threshold level) capable of eliciting a barely recordable change in the impedance of the tympanic membrane of the other ear Th intensity was increased by 2 dB teps during each off interval

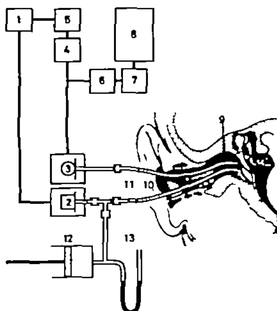


Figure 2. Block diagram of pparatus for analysing the changes f the acoustic impedance of the ear

1 Oscillator 216 Hz
2. Earphone
3. Microphone
4. Amplitude control
5. Phase control
6. Selective amplifier
7 Valve voltmeter
8. Recording apparatus (Brüel and Kjær level recorder)
9. Rubber plug
10. Polyethylen tubes
11 R bber cuffs
12. Pump (syringe)
13. Manometer

The changes in the acoustic impedance of the other ear were recorded using an electro-acoustic impedance bridge, (Madsen Electronics, Mod 1 ZO 61) originally designed by Terkildsen and Scott Nielsen (1960) and later modified by Djupesland (1961), the unbalance of which was registered on a Brüel and Kjær level recorder (2305 A), using a linear potentiometer. A block diagram of the apparatus is shown in fig. 2.

RESULTS

a. Threshold of the acoustically elicited impedance changes

The impedance threshold was investigated in 11 test subjects using frequencies of 250, 1000, 2000 and 4000 Hz. The results are shown in table 1 and fig. 3. The threshold was lowest for 250 Hz and showed a slight increase towards 4000 Hz. The standard deviation was least at 250 Hz and increased considerably with frequency up to 4000 Hz which was the highest tone investigated.

TABLE 1

IMPEDANCE THRESHOLD (MEAN VALUES FOR 11 SUBJECTS) AND STANDARD DEVIATIONS FOR STIMULUS FREQUENCIES 250 HZ—4000 HZ

Frequency	250	1000	2000	4000 Hz
Mean values	87.3	87.9	88	91.2 dB
2 S	11.4	17.4	18.4	23.6 dB

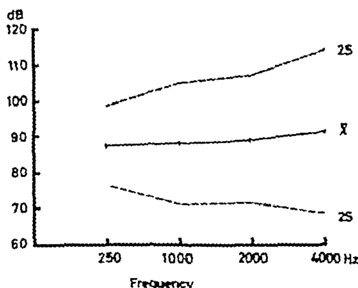


Figure 3. *Impedance threshold (mean values to 11 subject) and standard deviation as a function of frequency.*

The impedance threshold was determined for white noise and octave band of white noise in three test subjects. The test were repeated after at least 21 hours so that a total of 6 recordings were made. The results are shown in table 2. The threshold for white noise tended to be markedly lower than that for the octave band of white noise.

TABLE 2

IMPEDANCE THRESHOLDS F R VAR US TYPES OF STIMULI IN 3 UBJECTS A INTERVALS MORE THAN 24 HOURS

subject	stimulus									
	pure tones					octave band of whit noise				
	250	500	1000	2000	4000	(200—400)	(800—1600)	(3200—6400)	whit noise	Hz
T S.	78		81	84	81	76	74	67	56	dB sensation level
	73		78	81	85	75	73	73	56	
S. B.	89	90	90	84	95	86	86	81	78	
	89	92	88	86	97	84	82	79	78	
A. L.			82	72	83	82	74	65	60	
	89	90	82	4	77	82	76	73	68	

b Size of the elicited impedance changes

As shown in fig 4 there was a marked difference in the size of the impedance changes elicited by tones of frequency 250 Hz from those of 4000 Hz. For the stimulus frequency of 250 Hz there was a rapid increase of the size of the impedance changes as the sound intensity was increased above the impedance threshold. The maximal change in impedance was reached at a level of about 18 dB above the impedance threshold

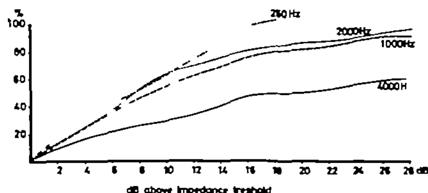


Figure 4. Increase of impedance change (measured in per cent of maximal impedance change) for different stimulus frequencies as function of increased stimulus intensity (dB above impedance threshold). Mean values for 20 subjects.

The increase of the impedance change with increased intensity of a stimulus tone of 4000 Hz was not nearly as large as for 250 Hz, and even at 28 dB above the impedance threshold the impedance change for 4000 Hz was not more than 60 to 70 per cent of the maximal impedance change for 250 Hz

For the stimulus frequenceis 1000 Hz and 2000 Hz the impedance changes were of about the same size when using the same stimulus intensity (dB above the impedance threshold). For identical stimulus intensities above the impedance

threshold the elicited impedance changes were considerably greater than for 4000 Hz and only slightly smaller than for 250 Hz.

The maximal impedance changes for 1000 Hz and 2000 Hz were furthermore about the same as for 250 Hz, although this impedance change occurred for a rather high stimulus intensity i.e. about 28 dB above the impedance threshold compared with 18 dB for 250 Hz.

The findings just described for these four stimulus frequencies were mean values for 20 subjects, and could be demonstrated in almost all the test subjects.

The increase in the impedance changes as a function of the increase in the stimulus intensity was greatest in the region 0—16 dB above the impedance threshold for all four frequencies. Above this level further increase of stimulus intensity had little influense upon the size of the impedance change.

c. Duration of the elicited impedance changes

This investigation was carried out for pure tones of frequencies 250, 1000 and 4000 Hz and for white noise and octave band of white noise ((200—400) Hz, (800—1600) Hz, (3200—6400) Hz). We used the same apparatus and method as previously described, only the stimulus was not interrupted, but made continuous.

The duration of the impedance change elicited by pure tone stimuli was investigated in 11 individuals. The intensity of the stimuli was 10 dB above the impedance threshold for the frequencies 1000 Hz and 4000 Hz. However for the frequency of 250 Hz the limited capacity of the apparatures (low harmonic distortion necessary) meant that a somewhat lower intensity had to be used in most of the test subjects.

The results are shown in table 3 and an example for one subject is presented in fig. 5 a.

A continuous stimulus tone of 4000 Hz did not maintain an impedance change for more than a short time (0—70 secs). A tone of lower frequency could maintain an impedance change considerably longer. Using a continuous stimulus tone of 1000 Hz an impedance change lasting from 22 to 137 seconds was recorded.

TABLE 3

DURATION OF IMPEDANCE CHANGE, ELICITED BY A CONTINUOUS PURE TONE STIMULUS OF INTENSITY LEVEL 10 DB ABOVE THE IMPEDANCE THRESHOLD

subject	stimulus			
	250 Hz	1000 Hz	4000 Hz	
P. H.	>135	77	4	time in seconds
F. F.	>127	80	1	
S. K.	>168	>133	70	
F. L.	>133	123	27	
D. T.	>133	60	3	
R. K.	>168	32	20	
E. T.	>145	78		
G. B.	>153	87	11	
L. F.	>173	137	10	
C. D.		163	23	
F. S.	>167	22	28	



Fig. 5 a.

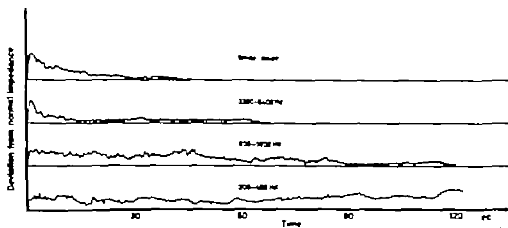


Fig. 5 b.

Figure 5. Duration of impedance change elicited by various continuous pure tone stimuli ( ) and bands f whit noise (b), intensity level 10 dB above the impedance threshold (1 subject).

When a stimulus frequency of 250 Hz was used, the impedance change could be maintained for such a long period that the test was stopped before there was any obvious reduction of the size of the impedance change (127—168 secs.)

The duration of the impedance changes elicited by continuous stimulation with white noise and octave bands of white noise was investigated in three subjects. The intensities of the stimuli were 2, 4 and 10 dB above the impedance threshold. The results are shown in table 4 b and an example for one subject is presented in fig 5 b

These results were not uniform and the number of cases was small. However it seems that a low frequency octave band of white noise will maintain an impedance change over a longer period than does a high frequency octave band (3200—6400) Hz.

The duration of the changes in impedance in relation to the intensity of the stimulus during continuous stimulation with pure tones, white noise and octave bands of white noise was investigated in three subjects. The intensity of the stimulus used was 2, 4 and 10 dB above the threshold of impedance. The results are shown in tables 4 a and b There is an obvious tendency for increasing stimulus intensity to give increasing duration of the impedance change An example using white noise is presented in fig 6.



Figure 6. Duration of impedance change elicited by white noise of intensity level 2, 4 and 10 dB above impedance threshold (1 subject)

DISCUSSION

The apparatus was checked several times in the course of the series of experiments and was found to be stable within ±1 dB The attenuator settings were checked acoustically by measuring the variation of sound pressure in the earphone on the IEC coupler and correlating this with the respective attenuator settings. In one of the outer extreme settings of the attenuator there was not satisfactory correlation between the nominal steps and the variations in sound pressure recorded However we only used the sound pressure readings recorded on the coupler at the respective attenuator settings.

The purity of the stimulus tone naturally varies with the level of sound pressure. At the level of the threshold of impedance the harmonic components were more than 30 dB below the level of the basic tone, and at maximal intensity the difference was 20 dB or more

The Electronic Switch functioned without any overshot.

The white noise stimulus has its spectrum formed by the response curve of the earphone i e. substantially flat up to 6000 Hz (fig 7)

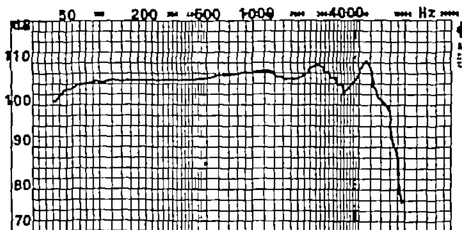


Figure 7 Frequency response curve of the headphone used (PDR 8).

The octave bands of white noise fell off with 30 dB per octave to each side.

The stability of the apparatus is reflected in the reproducibility of the results in the same subjects on different occasions.

TABLE 4 a and b

DURATI… IMPEDANCE CHANGES FOR V…RIOUS TYPES OF STIMULI AN… …ARIOUS LEVELS … STIMULUS INTENSITIES IN 3 S…BJECTS AT INTERVALS … N… …RE THAN 24 … …URS

a

type of stimulus		250 Hz			500 Hz			1000 Hz			3000 Hz			1000 Hz			
stimulus intensity dB above impedance threshold		2	4	10	2	4	10	2	4	10	2	1	10	2	1	10	
subject	T. S.	>180 >180	>180 >180	>180 >180				>180 96	>180 162	>180 >180	107 >180	266 >180	280 >180	26 >180	10 >180	60 >180	time in seconds
	S. B.	>180 >180	>180 >180	>180 >180	28 18	53 39	133 >121	18 11	28 65	60 50	4 1	3 7	7 24	2 3	3 3	3 4	
	A. J.	 60	 >180	 >180	11 >180	>180 >180	>180 >180	173 26	>180 80	>180 >180	18 6	30 13	61 78	3 0	5 1	11 10	

b

type of stimulus		(200—100) Hz			(800—1600) Hz			(3200—6100) Hz			white noise			
stimulus intensity dB above impedance threshold		2	4	10	2	1	10	2	1	10	2	4	10	
subject	T. S.	>180 >180	>180 >180	>180 >180	>180 >180	>180 >180	>180 >180	>180 160	>180 193	>180 >180	>180 103	>180 78	>180 194	time in seconds
	S. B.	163 1	>180 33	>180 >180	17 13	118 >123	>180 >180	66 0	03 1	15 11	15 15	13 30	>180 106	
	A. J.	12 >180	161 >180	>180 >180	>180 25	>180 >180	>180 >180	100 33	80 >180	>180 >180	128 >180	16 15	>180 73	

The recording of the changes in impedance was performed with a linear potentiometer in the Brüel & Kjær Recorder In this way the impedance changes were recorded with about the same intensitivity as that of the indicating instrument on the impedance bridge, though with a greater range of recording

An important question that arises in this investigation is whether the results obtained are reproducible. The tests were therefore repeated in three of the test subjects after at least 21 hours. It appeared that the values obtained for the impedance threshold showed little difference from one time to the next (table 2). The reproducibility was also shown to be very good in the investigation of the size of the elicited impedance changes. The results of measuring the duration of the impedance changes during continuous stimulation with pure tones were found to be reproducible in most cases (table 4 a) The results obtained for continuous stimulation with white noise and octave bands of white noise were extremely variable and the reproducibility rather poor in most cases (table 4 b)

The volume of the space limited by the tympanic membrane, the auditory canal and the plug in the auditory canal varied slightly from one test subject to another In order to determine whether this variations affected the results, the impedance threshold and the size of the elicited impedance changes were investigated twice in three test subjects, once with the plug rather far out in the auditory canal and once with the plug much nearer the tympanic membrane. The change in the position of the plug was shown to have no effect either on the impedance threshold or on the percentage increase in the size of the impedance change

It therefore seems obvious that the reflex mechanism of the middle ear behaves distinctly different when the ear is stimulated with sound containing most energy in the low frequency range compared with sound of high frequencies.

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DISCUSSION

E. D. Neergaard Brabrand Denmark to Salomon

I the further t dies f these reflex manifestations also a quite different technique may be used. When continous tone is applied to the skull microphone may detect the tone by air onduction in the ear canal. The microphone signal will among other factors also depend on the ound conducti g system of the middle ear and hence it is possible to detect shift in phase and mplitude corresponding to changes i the middle ear mechanism .g. caused by reflex con tractions of the tympani muscles. Th procedure is however not fully developed yet.

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IMPROVED METHODS IN BONE-CONDUCTION AUDIOMETRY

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The interaural attenuation in bone- and airconduction measurements have been evaluated on 50 monaurally deaf subjects using different type of sound sources. The results of the investigation applied on BC audiometry point at narrow-band noise masking through insert receiver being superior to regular headphones. Modification of the SAL-method is discussed in order to eliminate the disadvantage of the occlusion effect.

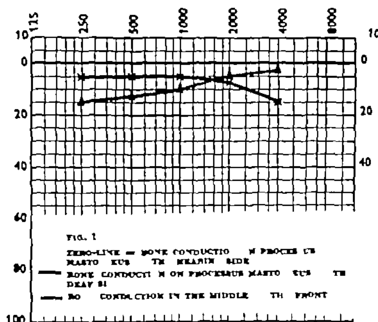
The condition of the inner ear is of decisive importance for the final result of stapes surgery and tympanoplastic operations. The clinical evaluation, of the function of the inner ear is based on the results of the bone-conduction (BC) measurement, as well as upon discrimination and recruitment tests. The BC threshold is frequently considered of major importance.

The BC threshold measurement however entails several elements of uncertainty which tend to lessen the reliability of the results. As an example it may be mentioned that tones from the BC vibrator when placed on the mastoid process on one side, simultaneously stimulate both the inner ears at approximately the same strength, this giving rise to masking troubles. If the customary method of investigation, using ear-phones for masking purposes is applied, the minimum effective masking level will often exceed the maximum usable masking level which by reason of the so-called cross masking, will cause deterioration of the bone conduction of the ear being tested. This, in turn, renders an evaluation of the function of the cochlea more difficult — a fact which is particularly pronounced in cases with bilateral conduction losses. The extent of the contact surface covered by the masking phone in use is of great importance for cross hearing. The larger the contact surface the lower becomes the transcranial attenuation. Thus many authors have suggested the use of hearing-aid-type insert earphones. (Zwislocki 1953 Palva & Palva 1962.)

With the object of improving the reliability of the BC measurement, we have examined 1) the effect of different ways of locating the vibrator 2) the possibility of increasing the intra-aural sound attenuation by means of insert earphones, and 3) the usefulness of the Jerger Tillman so-called SAL test. The investigation has involved 50 monaurally deaf patients, as well as 25 patients (50 ears) with normal hearing

1) In order to find most appropriate spot for locating the BC vibrator a comparison was made in the monaural deaf group between the BC thresholds on the mastoid process of the hearing side, on the forehead and on the deaf side and between these three BC thresholds and the air-conduction threshold of the hearing side During the BC tests, both ear canals were left unoccluded.

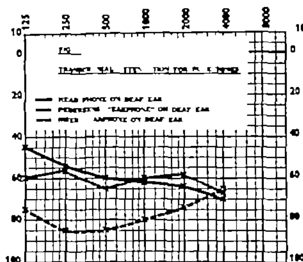
The results are shown in fig 1 The average transcranial attenuation from the mastoid process of the deaf ear is 5 dB in the frequency range 250—2000 Hz and 15 dB for 4 000 Hz. In the comparison between the BC threshold sensitivity measured on the mastoid process of the best ear and the centre of the forehead it was found that the threshold in the forehead was from 5 to 15 dB higher than on the mastoid process The standard deviations of the differences between BC thresholds of the mastoid process of the normal ear and the deaf ear and the forehead respectively were found to be between ± 7 and ± 11 dB for different frequences. Thus in a certain number of cases it can be anticipated that the response may arise in the non tested ear at a level of from 5 to 10 dB — and in some cases even up to 15 dB lower than the ear actually on test

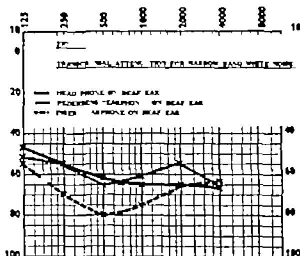


As far as locating the BC vibrator over the mastoid process is concerned, even the slightest displacement of the position of the vibrator gives rise to notable variations of the BC threshold. From this point of view the application of the vibrator in the middle of the forehead, a centimeter or two above the eyebrowe, will provide for a much more stable reading If the air conduction threshold of the group of monaural deaf subjects is compared with the BC thresholds of the mastoid process of normal side and the forehead the standard deviation of the threshold differences could be regarded as a certain criterion of the reliability of the method However the standard deviation was approaching ± 9 dB for both Similar tests have been carried out on 50 ears with normal hearing the untested ear being masked 30 dB by a narrow band white noise via insert earphone The standard deviations of difference between the air conduction threshold and BC threshold on the mastoid process and in the forehead were found to be ± 6.8 and ± 7.4 dB respectively From this it follows that the reliabilities of the methods

in this respect are of equal value As previously mentioned, on the other hand it appears from fig 1 that in order to attain the BC threshold in the forehead it requires a 5—15 dB higher sound intensity than over the mastoid process. The measuring range of the audiometer will thus be restricted and BC thresholds above 55 dB will be difficult to measure

2) The intra-aural attenuation of 50 monaural deaf subjects has been subject to test in respect, of pure tones and narrow band white noise when using different earphones a. Headphone type Telefonic, TDH-39 fitted into MX 41/AR cushions, b insert phones of hearing aid type and c. M. P Pedersen's loudspeaker mounted into spherical containers and having a capacity of about one litre Fig 2 shows the results when stimulating the deaf ear with pure tones. In the frequency range 125 to 2 000 Hz the insert phone was superior varying between 33 and 10 dB In





respect of the frequency of 4 000 Hz, the insert phone was 7 dB inferior to that of the earphone

In fig 3 the intra-aural attenuation of narrow band white noise stimulating deaf ear is demonstrated. This is accomplished by comparing the differences in the masking attenuator reading on the deaf and the good ears giving a threshold shift for pure tones of 10 dB With the insert phone, the attenuation was approximately 15 dB higher than that with the earphone and the Pedersen s searphones

In summation it can be stated that masking with the aid of insert earphone entails less risk of cross masking with consequently increased reliability of the BC threshold measurement.

3) In 1960 Jerger & Tillman published their so-called SAL method — sensori neural acuity level. The shift of air-conduction thresholds for pure tones by masking noise applied by means of a BC vibrator attached to the forehead in patients with hearing losses are compared with those of normal hearing subjects. The difference constitutes the BC threshold of the patient.

One of the most weighty objections against the SAL method is that it involves occluded BC thresholds, which makes it difficult to distinguish between conduction and sensory neural losses. This has also been our experience.

In the case of the earphones used by Jerger & Tillman on application of the SAL method — TDH 39 — the effect of occlusion according to Elpern and Naunton 1963 averaged 28 dB on 250 Hz, 30 dB on 500 Hz and 9 dB on 1 000 Hz, whereas no occlusion was recorded on 2 000 Hz and higher frequencies. The effect of occlusion is characterised by a very wide standard deviation, not only between different individuals, but also in one and the same subject on test — retest. Elpern and Naunton showed that the occulusion effect could be avoided by using earphones operating with a large volume of air and consequently we tested the effect of occlusion of Pedersen s spheric searphones not only on 50 ears with normal hearing but also on 50 monaural deaf patients, by comparing the BC threshold measured on the forehead with the phones connected as well as leaving the ears free The average effect of occlusion with respect to the 100 ears tested with Pedersen s type of earphones is shown in Table 1

TABLE 1

AVERAGE OCCLUSION EFFECT IN DECIBELS PRODUCED BY PEDERSEN'S LOUDSPEAKERS IN SPHERICAL ENCLOSURES ON 100 NORMAL EARS

250	500	1 000	2 000	4 000
0.15	0.6	0.3	0.55	—0.45

It was thus found that the occlusion effect with Pedersen s type of earphones was negligible.

We then examined the importance of the occlusion effect in the use of the SAL method by establishing a comparison between Pedersen s type of phone and ordinary earphones. In this investigation we used white noise as Jerger & Tillman, and also narrow band white noise On an average we found the effect of occlusion

to be between 8 and 12 dB on frequencies from 125 up to 1 000 Hz in the case of white noise as well as narrow band white noise, whereas no occlusion effect could be noted on frequencies of 2 000 and 4 000 Hz. As established by Elpern and Naunton we also found that the standard deviation of the occlusion effect was of considerable magnitude. When applying the SAL method, the effect of occlusion, is manifested by amplification of the noise from the forehead thus, at the same time amplifying the masking effect. This makes it easier to get a sufficient shift of the airconduction threshold using regular headphones but is a drawback using Pedersen's earphones. In fact using Pedersen's earphones and a commercial BC vibrator as masker we have not yet been able to get a sufficient high threshold shift to make the method clinically useful. However with improvements of the BC-vibrator the SAL method seems very promising.

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A NEW INDIVIDUAL NOISE DOSIMETER

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Noise induced perceptive hearing loss is due to noise frequency noise intensity time of exposure and also to individual noise sensitivity Hitherto it has only been possible to analyse the frequency and intensity during different moments of work with the aid of conventional noise meters.

Th individual time f exposure has therefore as a rule only been estimated approximately As a worker very ften is moving around in a factory the noise may be altered from time to time Thus the need of an individual, continual regi tering of noise for each individual worker during several weeks or months is obvious.

This aim is now possible to reach with the aid of a new pocket-sized registering apparatus, designed at the ENT Dept, General Hospital, Malmö and which is meant t be worn by especially noise-exposed workers. Its prophylactic importance is analogous to the film dosimet rs used by persons exposed to ionizing radiation and it has therefore been called noise dosimeter

An extensive use of th apparatus is thought t be of prophylactic and medical importance and may lead to: 1) a greater individual interest for noise prophylaxis, 2) an effective industrial noise supervision and 3) a more adequat medical control of noise sensitive — or already noise-damaged patients.

In modern time noise has become an increasing social and medical problem It has by itself great individual psychologic influences but the irreversible hearing loss is always the most deleterious problem. Several factors contribute to the development of a noise-induced hearing loss. The individual susceptibility and the characteristics of an actual noise constitute the main groups of etiologic factors. From a hygienic, social and medical point of wiew the noise ought to be analysed according to

1 Noise frequency
2 Noise intensity and
3 Duration of exposure (the third factors)

It is clinically and experimentally well known that noise of high frequencies more often gives rise to a hearing loss than noise of low frequencies. This factor can easily be checked by means of octave band analyses.

The intensity of noise is generally spoken of as the most important risk factor In this respect however the individual susceptibility varies within wide limits. Numerous investigations on damage risk criteria viz. noise intensity have been published and a rather great variation in tolerance has been accepted (Burns, Chadwick Dickson, Clorig Laden et al. Oppliger et al Sataloff etc.) From a practical point of wiew howe er it is necessary to predict a form of noise tolerance limit Such a limit of 85 dB (re 0 0002 dyne/cm^2) has also been accepted in the United States, England and Sweden The noise intensity factor can be measured by conventi nal noise meters (Fig 1).

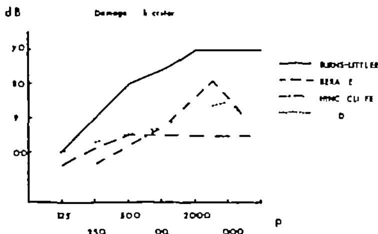


Fig. 1 Damage risk criteria according to Burns and Littler Beranek Hinchcliffe and Hardy Ordi ta: dB sound pressure level. Abscissa. octave band frequency (cit. Kylin).

Which is the exact dose of injurious noise that a person e.g an industrial worker is exposed to during a day or a week? This question is of great importance in evaluating the potential risk for a hearing loss. It has, however hitherto, been difficult to estimate this factor with the same accurateness as the frequency and the intensity The latter may vary within wide limits from time to time also at a fix working place and a worker may be occupied near different noise sources during the day Such circumstances make it difficult to measure the exact individual dose of noise or time of exposure By the aid of different tables some authors (Glorig and Nixon Kylin) have tried to evaluate the maximal allowance of noise exposure for some special kinds of workers. Such analyses give a rather good approximative evaluation of »the third factor» but this approach is time consuming and not very exact

In order to overcome these difficulties a special apparatus has been constructed (Toremalm) It consists of a microphone, a transistorized amplifier an electric motor and a counter for time marking or more exactly measuring the incoming sound energy (noise dose) (Fig 2 and 3)

The dimensions of the apparatus are 10 × 9 × 3,5 cm and it weighs 300 grams. It is therefore easily worn in a pocket of the overalls. It is called *noise dosimeter* analogous to the film dosimeters which are prophylactically used by people exposed to ionizing radiation.

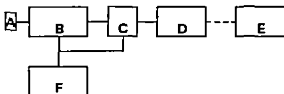


Fig. 2. Block diagram illust ting th noise dosimeter A microphone B. transistorized amplifier C switch transistor D electric motor E mechanic counter F dry batteries.

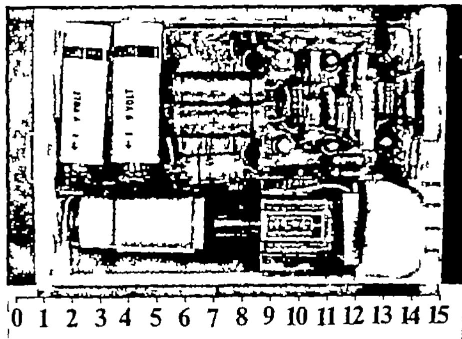


Fig. 3. Noise dosimeter from above mounted in a perspex cover for demonstration.

The apparatus can be adjusted for different intensities e g from 70 to 100 dB dependant on the desired tolerance level. Naturally it can be provided with still more advanced electric units but the ones chosen seem to be good enough for practical use The microphone, for example is of a dynamic type (ELFA B 512) in the preliminary series but some reasons favour the use of a crystal type of microphone It has a relatively good capacity of registration within the actual frequencies of 500—8000 cps. It may be considered that the microphone from a practical point of view is placed about 30 cm from the ear but it is possible to separate the microphone from the apparatus and place it near the ear The amplifier is transistorized (four transistors type OC 75) and it is fed from two parallelly connected dry batteries of 9 volts each The 3 volt eletric motor (Dunker GK 10 ZG) has a built in gear for speed reduction of 500 1 and it starts when the noise level exceeds the desired dB-level. The registration takes place as long as the noise exposure continues. Even noises with a short duration e.g 1 sec. or less can be registered Start and stop take place nearly instantaneously In the preliminary model the motor accelerates with increasing noise intensity above the desired level in such a way that the registered value is a product of duration and intensity (= the dose of noise) which means that the amount of undesired sound energy will be measured It is, however technically possible to change the amplifier so that it will work continuously also above the level of tolerance without any acceleration. In this version the real exposure time can be registered but then the apparatus must be bigger and therefore less practical. The amount of incoming undesired noise can be estimated from the counted figures with the aid of standard tables. A test curve is shown in figure 4

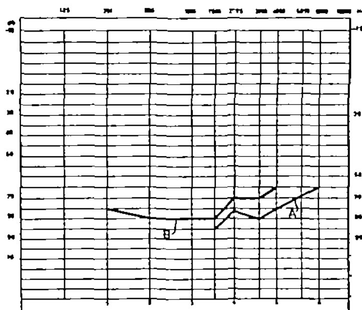


Fig. 4 A free-field test curve with the preliminaryly chosen microphone. A. White noise with different supporting pure tones. B. Pure tones alone.

The apparatus is adjusted to work at the 75 dB level and is tested with pure tones in free field (A) and with »white noise» combined with supporting tones (B) With the preliminary chosen microphone the noise dosimeter is somewhat more sensitive at frequencies above 1500 cps than below Thus it will start at a lower intensity for more deleterious frequencies.

Earlier experiments with the intention to measure individual noise exposure have been described (Church, Estes Benson) According to Church, who has worked on this problem at Esso Research and Engeneering Company for six years, all previously described devices are too large, too complex and too costly to make them clinically or practically usable He described in 1965 his own model which consists of a microphone, an electric circuit and an ampere-hour meter for time registering The latter is however temperature dependent and easily breakable for as little as 21—50 gram chock. Also too high a current may destroy the ampère-hour meter The whole apparatus is worn in a leather belt which may be inconvenient for some workers. Such problems do not seem to limit the use of the present noise dosimeter

The new approach to analyse the third factor» in the fight against noise-induced hearing loss has not been dealt with earlier in otologic literature as fas as we know The present introduction makes further experiments necessary Investigations for practical utilization of the noise dosimeter are in progress. In addition to the theoretic value a widespread use of the apparatus seems to be of medical as well as practical hygienic importance which may lead to·

a greater daily individual interest in noise prophylaxis

a more effective industrial noise supervision and

a more secure medical follow up of noise susceptible or already noise injured patients.

The authors wish to express special thanks to engineer H Ericsson for valuable assistance [illegible] manufacturing the noise dosimeters.

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THE CLINICAL AND AUDIOLOGICAL PATTERN DUE TO ACOUSTIC TRAUMA.

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The present study describes the results of investigation carried out on 355 ears with acoustic trauma caused by gun noise. The methods used were pure ton audiograms, speech udiometry Reger' monaural recruitment-test, threshold tone decay test (perstimulatory adaptation) and registration of poststimulatory fatigu and diplacusis phenomenon.

The material has been classified in four various degrees of hearing loss. By means of mentioned udiological tests the auditory function of the damaged ears is analysed in various stages of acoustic trauma.

The hearing loss caused by sound stimulus is called acoustic trauma (AT) A clinical and audiological analysis has been done on the material of the present investigation. The material consists of armed forces personnel, Table 1 Though comparable investigations are missing, it is probable that the clinical and audiological pattern due to acoustic trauma is almost similar in different etiologic groups. As known, there must be continuous noise intermittent noise or short shock waves as detonations, as reason for AT

TABLE 1

M TERIAL

Normal hearing	140	33.. %
Acoustic trauma	241	57.2 %
Other ear diseases	41	9.6 %
(Total)	422	100.0 %

We can classify the pure tone audiogram by AT in three main types, Fig 1 The occurency frequency of these types is given in per cent The average curves for the whole material are described in Fig 2. The first quartile (Q_1) shows the hearing loss of the poorest 25 of the hearers, Q_2 the median, and Q_3 the best 25 of the hearers respectively *The greatest reduction of hearing appears at 5 500 cps.*

In order to better be able to examine the development of the clinical and audiological pattern in different stages of AT the material has been devided in four degrees of severity The pure tone audiogram has been the objectiv basis for all classification The presbycusis-corrected audiograms are graded for degree of hearing loss as follows:

degree I — hearing loss of 15—30 dB at 3 000, 4 000 6 000 or 8 000 cps

II — hearing loss of 35—60 dB at 3 000, 4 000 6 000 or 8 000 cps

III — hearing loss over 60 dB and/or comprises partly the speech range the range between 500 and 2 000 cps in the pure tone audiogram. An AT of the III degree is lasting, which appears from the average curves.

VI — hearing loss occurs also in the lower frequencies

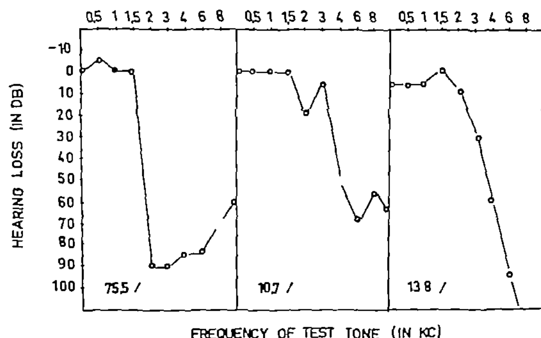


Fig. 1 The three main types of the pure tone audiogram by acoustic trauma. The occurence frequency in per cent.

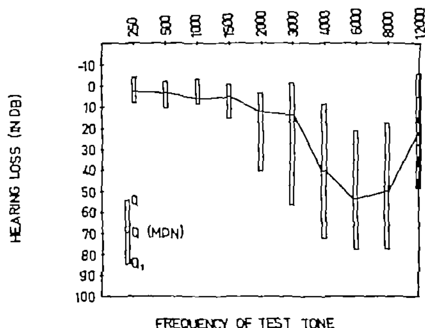


Fig. 2. The average curves for th whole AT material. See text.

The most important function of the ear is its ability to understand everyday speech Table 2. For the whole material the speech reception threshold has remain quite normal for more than 80 per cent of all the persons injured by detonations. The discrimination ability for speech generally also remains in severe AT Table 3 93 per cent of the whole material had a normal articulation score

TABLE 2

SPEECH RECEPTION THRESHOLDS IN DIFFERENT GROUPS OF SEVERITY

SRT (in dB)	Groups of severity			
	I	II	III	IV
≤10	42	94	146	3
11–20	1	5	40	8
21–30			1	5
>30				9
Total	43	99	187	23

TABLE 3

DISCRIMINATION ABILITY IN DIFFERENT GROUPS OF SEVERITY

D. A. *(per cent)*	Groups of severity			
	I	II	III	IV
100–90	43	98	173	16
89–80		1	10	4
79–70			4	3
50				1
15				1

The AT has been more exactly analysed by examining the recruitment phenomenon with the monaural method by Reger the perstimulatory adaptation with threshold tone decay tests by Carhart, and besides the poststimulatory fatique. All these test have generally been examined on 3 frequencies at half an octave intervals.

The function of the recruitment phenomenon is described in Table 4 Above all the great part of the incomplete recruitment phenomenon is worth attention If we examine the function of the recruitment phenomenon in different groups of severity that is, in different stages of development, we can certify that in the first stage of AT the loudness recruitment is generally complete. Whereas, in more severe cases the recruitment-phenomenon gets incomplete. A very highly significant change of the function of the loudness recruitment phenomenon occurs statistically in connection with the development of the AT

TABLE 4

RESULTS OF THE LOUDNESS RECRUITMENT TESTS

Overrecruitment	3.6 %
Complete recruitment	40.1
Incomplete recruitment	48.4
No recruitment	7.9
(Total 963)	

Perstimulatory adaptation has been classified according to Sörenssen as normal (less than 10 dB), or as pathologic (more than 30 dB, or the type, in which the threshold is continuously decaying and not reaching a plateau). The results are given in Table 5 During the adaptation test the subjective quality of the stimulating

tone may change, generally into soughing This diplacusis, is a quite general phenomenon If we compare with one another the amounts of adaptation in different groups of severity we can establish that in the first stage of AT the adaptation is insignificant normal or almost normal. In more severe cases the adaptation increases, although it quite seldom gets clearly pathologic. Statistically this change occurs highly significant

TABLE 5

AD PTATI N

Normal	31.2 %
Pathologic	15.4 %
Average	16.2 dB
Diplacusis	40.2 %
(Total 963)	

Between the recruitment-phenomenon and adaptation there is no correlation which also clearly appears from Fig 3 Here the biggest point corresponds to 10 cases, the medium-sized to 5 cases, and the smallest to 1 case

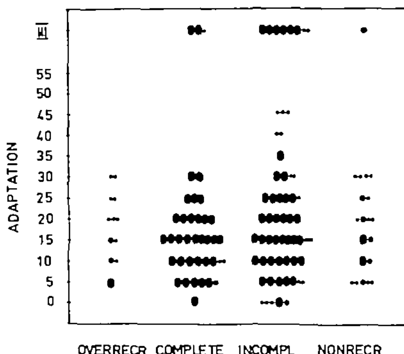


Fig. 3. Distribution of 963 frequencies (in 355 ears) ccording to loudness recruitment f ction in relation t the mou t (and III type of Sorensen) of adapt tion The biggest point = 10 cases, the medium-sized = 5 cases, the smallest = 1 case

On the same frequency as the recruitment phenomenon and the adaptation the poststimulatory fatigue is also examined It exists in all the development stages of the AT by about 30 per cent It is not connected with any type of recruitment or

adaptation. Besides, in the same ear on different frequencies, there can be or not to be fatigue. The clinical value of poststimulatory fatigue is uncertain In the first pla e it will reflect the prognosis of the hearing threshold at the examined frequency

If we accept the idea, that the recruitment-phenomenon is a symptom for that the hearing loss is located in the end-organ, and that the adaptation, on the other hand, is typical of the retrocochlear deafness, we can establish that the audiological pattern of AT corresponds quite well with the prevailing morphologic changes.

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HEARING AND PRIMARY AUDITORY CENTRES OF THE WHALES

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Neurophysiological investigations performed during the later years have thrown light upon the exceptional auditory abilities of the whales. This report shortly recapitulates earlier findings and outlines the general structure the microscopic appearance and the number of cells in the cochlear nuclei of some whale species. The number of cells are compared to the number of fibres in the VIIIth nerve

Also these anatomic features indicate a highly specialized auditory system.

In recent years quite an amount of research has been performed concerning the acoustic system in whales. Their unique performance in the depths of the oceans has attracted the interest of various fields of medicine, expecially morphology neurophysiology and otology (Hatcheck and Schlesinger 1902, Langworthy 1932, Jelgersma 1934 Ogawa and Arifuku 1948, Sheffield and Lawrence 1953 1965 Kellogg 1953 McBride 1956, Reysenbach de Haan 1957 Griffin 1958 Lilly 1961 Osen and Jansen 1965) We are now aware that at least some of the whale species are capable of echolocation, and possibly intercommunication. In applying a conditioned reflex system to sound stimuli of various frequencies, Sheffield and Lawrence (1953) showed that the Bottlenose-dolphin was capable of detecting frequencies up to 153 000 cps, and their vocal apparatus is anatomically well equipped for producing high pitched sounds under water These peculiar features in the whales favour the echolocalization as smaller objects can be distinguished and localized more accurately with the short waves they are able to employ

It is of interest to see, how this extraordinary function is reflected in the structure and microscopical appearance of the different sections in their auditory pathways. The cochlea will only be mentioned briefly primarily because the author's main interest hitherto has been in the cochlear nuclei, but also on account of the fact that earlier methods did not yield satisfactory results. However this organ will be studied more thoroughly in collaboration with Engström and Bredberg in Gothenburg At present a picture is shown, giving a macroscopical view of the cochlea in a 5 foot fetus of a blue whale (Fig 1)

The length of the basilar membrane in this case was 102 mm compared to the 34 mm usually found in Homo

It is also of importance to remember that in whales the basilar membrane is quite narrow throughout its length, on account of the lamina spiralis ossea being wide throughout the cochlea (Reysenbach de Haan 1957)

The bifurcation of the eight nerve is seen in Fig 2. The nerve is dividing into ascending branches to the anterior part of the nuclei and descending branches to the posterior part The ventral nucleus is by far the greatest part in the white whale

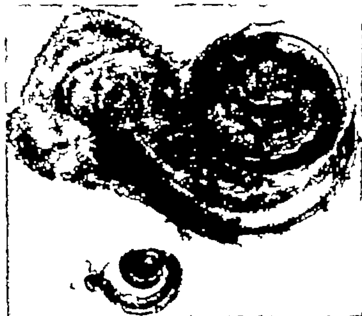


Fig. 1 Cochlea from blue whale f tus, 5 feet, compared t human cochlea. The basilar membrane in situ. The organ f Corti is seen as black ribbon. (Surface preparation by Bredberg.)



Fig. 2. The cochlear nerve entering the ventral cochlear nucleus. pA = pars anterior pP = pars posterior. Myelin stain. (Osen and Jansen 1965).

it contains about 75% of all the nerve cells. The greatest cells are situated along the nerve root, the smaller ones along the periphery As a rule they show the characteristic features of the nerve cells of the cochlear nuclei common also in man, they are round or oval, with a centrally situated nucleus richly surrounded by cytoplasm. An interesting finding however was the giant cells seen in the dorsal part of the anteroventral nucleus, (Osen and Jansen 1965) This finding may be of special interest to otologists, as earlier evidence points to this part as a localization area for high tones, (Rose Galambos and Hughes 1959) Also the dorsal nucleus is of special interest as its relation to hearing has caused much discussion in the literature. It is now agreed that within the cochlear nuclei the frequency sensitive neurones are arranged from high to low in an essentially dorsoventral sequence (Lewy and Kobrak 1936, Galambos 1951 Rose et al. 1959). The earlier prevailing opinion that the high tones should be located in the dorsal nucleus only has been corrected. This also agrees with the findings in the whales, where the dorsal cochlear nucleus is small, almost rudimentary It seems to become more reduced in the higher primates. In the cat it is quite differentiated with the cells lying in distinct rows or laminae, a distinction which is not present in Homo and in whales only a rudimentary rest can be detected, containing some spindle formed cells, but mostly very small ones. Such a small nucleus corresponds poorly to the pronounced high-tone performance in the whales.

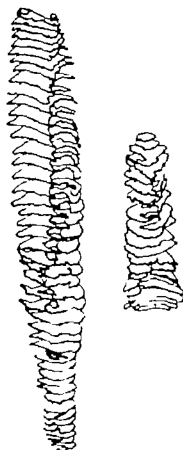


Fig. 5 The cochlea ciei in a small porpoise (left) compared t those f a 1½ year old child. Serial sections. E ery 10th section is drawn. Same magnification in both species.

The ventral cochlear nucleus, however situated between the medulla and pons, is in the whales from 6 to 32 times as voluminous as in Homo These facts are obtained applying a method described elsewhere, (Hall 1964). Serial sections of the nuclei are drawn, their area measured by planimetry and the volume de ducted Drawings of the serial sections are seen in Fig 3. where the cochlear nuclei in a young porpoise are shown, compared to those of a 1 1/2 year old child

The next figure (Fig 4) shows the calculated volume of the cochlear nuclei in some whale species compared to the average volume in man. The figures clearly indicate that the acoustic system in the whales is far more developed than in man.

Volume of the cochlear nuclei (in mm³)			
Homo	Porpoise	Fin whale	White whale
10	60—100	205	320

Fig. 4

This, however is true not only concerning the volume of the nuclei, they also contain a correspondingly ample number of neurones. This number is found by counting the nerve cells in a certain volume of the nuclei, and then calculate the number of cells in the whole complex (Hall 1964).

In Fig 5 these results are shown. The number of cells in the cochlear nuclei of man are compared to those of the porpoise, the fin whale (Balaenoptera physalus), and the white whale (Delphinapterus leucas) While the two first whales have about 6—7 times as many cells in their cochlear nuclei as man, the white whale has 17 times as many It may be of interest in this connection to remember that the white whale is called »the canary bird of the oceans«, on account of its multifarious whistling sounds.

Species	Total	Dors.nucl.	Dors.nucl. per cent of total
Homo	96 400	25 400	26
Porpoise	583 400	40 200	7
Porpoise	718 900	72 000	10
Fin whale	704 300	—	
White whale	1 650 000	24 000	1,5

Fig. 5. The total number of cells in the cochlear nuclei of different whale species and man, compared to the number and percentage of cells in the dorsal nucleus alone.

Concerning the dorsal nucleus, the number of nerve cells corresponds to the microscopical findings.

While the dorsal nucleus in homo contains about 26 per cent of the cells in the cochlear complex, it contains only about 7—10 per cent in the porpoises and 1,5 per cent in the white whale.

Discrimination ability however does not only depend upon the number of neurones, but also on the number of nerve fibres carrying the impulses to the

neurones. It is therefore of interest to compare the number of nerve cells to the number of fibres in the cochlear nerve (Fig. 6) (Jacobs and Jensen 1964 Jacobs et al. 1964) The most striking point in this table is the fact that the whales primary auditory centres receive from four to eight times as many primary fibres from the cochlea

Species	No. of fibres 8th nerve	No of cell cochl. nucl	Fibres/cells
Homo	25 000	96 000	1/4
Porpoise	100 000	600 000	1/6
Fin whale	150 000	700 000	1/5
Whit whale	210 000	1 050 000	1/5

Fig. 6.

Each of these must be considered as an independant canal. Compared to the great length of the basilar membrane it seems reasonable to assume that the possibilities for frequency discrimination are substantially more advantageous in the whales than in man. Furthermore it is seen that this information can be treated with more detail already in the first synapse, as the incoming impulses are distributed to many more neurones. We have reason to believe that where there are many nerve cells, more information can be extracted and conveyed from a given signal.

The cochlear nuclei constitute the first relay station in the auditory pathways. In the whales there is, as appears from the tables, a great number of primary fibres and, moreover a greater number of secondary cells pr primary fiber in the cochlear nuclei.

The most reasonable interpretation of these observations seems to lead to the conclusion that also in their central nervous system the treatment of incoming acoustic impulses is very advanced in the whales. This statement seems to be justi-



Fig. The superior and inferior colliculi in whit whale

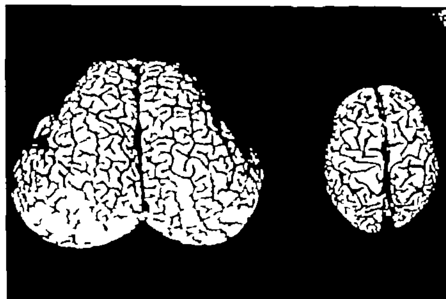


Fig. 8. The brain of Fin whale compared t the brain of man. Same magnification in both species.

fied also by the great development of the next big relay station, the inferior colliculi (Fig 7). They are bulging out on each side of the medulla far greater than the superior colliculi of the visual pathways, seen above. Also the temporal lobes of the whale brains, containing for one thing the auditory areas, are enormous (Fig 8). The auditory pathways of the whales still render abundant opportunities for future research. It is tempting, however already on the basis of the present findings to agree with the assumption that the whales must have a highly developed communication system (Lilly 1961) It is not surprising, that such a complicated function demands a pronounced development of the acoustic areas in the central nervous system

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OTOLOGIC AND OPHTHALMOLOGIC FINDINGS AFTER EXTRADURAL HEMATOMA

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Otologic and/or ophthalmologic abnormalities were found in 31 patients who had survived extradural hematoma. Since these findings can be of considerable medicolegal importance, neuro-ophthalmologic and otologic examination after extradural hematoma is essential.

Survivors of extradural hematoma have a relatively good prognosis. Lewin (1949) described the late results in 26 cases which were followed up for periods of two to eight years. All returned to full work or to school within two years. According to him improvement continues steadily for the first two years. During this time headache, lack of concentration, and nervousness are common. Residual effects of dysphasia and hemiparesis may still be apparent to the patient even if on routine examination, recovery seems to have been complete. Mental symptoms such as irritability, bad temper and poor concentration, gradually disappear. Three patients out of 26 continued to have attacks of severe depression. Four patients had fits while in hospital but have since been free over periods of two to six years. McKissock et al. (1960) examined 91 survivors of extradural hematoma. While of the 91 patients 63 had recovered and returned to full employment, school or normal occupation, 28 had not achieved full rehabilitation. Total physical or intellectual disablement was found in 8 patients. Disabilities of the following kinds were present: aphasia, hemiplegia, severe mental retardation in children, gross memory impairment, personality disturbance or chronic alcoholism. Partial disablement from hemiparesis, dysphasia, ocular palsies or uniocular blindness occurred in 16 patients and 4 patients had post-traumatic major epilepsy. Josephson (1962) described a series of 25 patients who had had extradural hematoma. 17 were entirely asymptomatic, 4 had mild symptoms at follow-up and 4 had severe persistent sequelae; only these last 4 were unfit for work due to the injury. Despite normal findings on routine neurologic examination, otologic or ophthalmologic deficit may occur. Troupp et al. (1964) found ear and/or eye abnormalities in all 17 patients who were followed. To elucidate this point further we collected more patients for otologic and ophthalmologic examination.

Material and methods

The 31 patients in this study were operated upon at the Neurosurgical Clinic, Helsinki University, during the period 1960—66, and a follow-up examination was carried out from 4 weeks to 4 years, on an average 2 years after operation.

Table 1 shows the age classification of the patients

TABLE 1

EXTRADURAL HEMATOM S CLASSIFIED BY A E O PATIENTS, 31 CASES

Age, years	Number f cases
1– 10	3
11—20	10
21—30	6
31—40	4
41—50	3
51 –60	4
61 –70	1
	31

The youngest patient was 8 years and the oldest 63 years old Average age was 29 years

There were 26 males and 5 females

A traffic accident was responsible for the extradural hematoma in 19 cases.

The hematoma was accompanied by a skull fracture in 23 cases.

Hearing was tested by pure tone and speech audiometry The caloric tests were performed with water at 30° and 44 C and nystagmus was recorded with an electronystagmograph Olfaction was tested according to the principles of Zilstorff — Pedersen (1957)

The follow-up ophthalmologic examination consisted of testing of visual acuity retinoscopy examination of ocular motility determination of the near point of convergence and ophthalmoscopy Special attention was paid to visual field studies. The fields were plotted by means of the Goldmann perimeter

Results

A Otoneurologic examination

The results of pure tone audiometry were classified by average thresholds for the frequencies 500 1000 and 2000 cps (table 2)

TABLE 2

HEAR NG FTER EXTRAD RA LMATOMA CLASSIFIED Y LRA THRESHOLDS FOR THE FREQ ENCIES 500, 1000 ND 2000 CPS 31 CASES

Decibels	No f cases	Comments
0—15	22	
16—30	2	Both homolateral
31 —45	5	Bilateral in 3 U lateral in 2: 1 homolat ral 1 cont alateral
46 60	1	Bilateral
61— 5		
6—90		
91—	1	Bilateral deafnes
	31	

As seen above, normal hearing was found in ¾ of the patients and only one patient had been deafened by the lesion.

Table 3 shows the results of the caloric tests.

TABLE 3

ELECTRONYSTAGMOGRAPHIC (ENG) FINDINGS AFTER EXTRADURAL HEMATOMA, 31 CASES

ENG	No. of cases
Symmetrical findings	
Normal reaction in both ears	4
Hypoexcitability in both ears	11
No response from either ear	7
Unilateral findings	
Hypoexcitability in homolateral ear	2
Hypoexcitability in contralateral ear	3
No response from homolateral ear	2
No response from contralateral ear	2
	31

Before the irrigation with water each patient was tested for spontaneous nystagmus in supine position, but none revealed spontaneous nystagmus nor did directional preponderance appear in the caloric tests.

The sense of smell was tested by determining the minimum perceptible odour (MPO). Normal values were found in 22 cases and disturbances in olfaction in 9 cases as follows.

bilateral hyposmia in 6 cases
unilateral hyposmia in 3 cases

Unilateral hyposmia, when present, was always on the side opposite to that of the hematoma.

B. *Ophthalmologic examination*

Visual acuity was generally good and the entire material included only one blind eye attributable to the severance of the optic nerve at the time of the accident. About one third of the patients exhibited disturbance of ocular motility. Three patients showed oculomotor nerve involvement of some degree and seven patients various changes ranging from bilateral ptosis to paralysis of convergence. The optic discs appeared normal in all except two patients. In one of these latter the changes were compatible with optic nerve severance and the other patient showed bilateral symmetric optic nerve atrophy.

The most significant changes became evident after the visual field examinations which were performed with the utmost care. Less than half of the patients (14) had normal fields, whereas the remaining series (17 patients) exhibited visual field changes varying from homonymous defects to concentric contraction. It should be noted that, of the patients who showed visual field changes, 65 per cent had normal visual acuity and there were no good reasons to expect visual field

defects after routine eye examination These changes were of considerabl medicolegal importance to the patients

Two illustrative cases are described here more closely:

Case 1 A 18-year old male had suffered a fracture of the right temporal bon in a traffic accident with resulting unconsciousness for 9 days. An extradura hematoma was evacuated from the right temporal lobe. On follow-up examina tion three months after the operation, rhinologic and vestibular functions as wel as hearing were found to be normal The ophthalmologic examination reveale normal findings apart from slightly lowered right visual acuity Visual fiel examination however revealed a left homonymous hemianopia compatibl with the site of hematoma (figure 1)

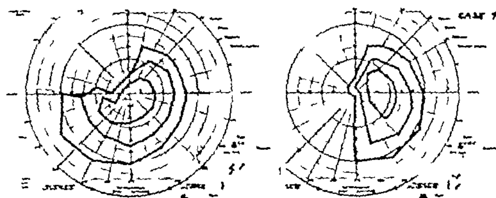
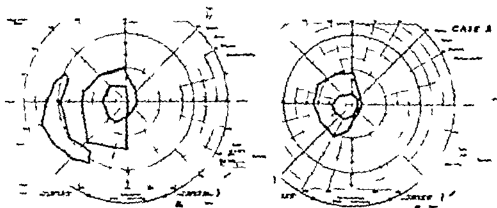


Fig. 1 Case 1 Left homonymous hemianopia after extradural hematoma.

Case 2 The patients was a 42 year old male who had substained a fracture o the frontoparietal region as well as extradural hematoma in a traffic accident On follow-up examination two years after the injury both ears were foun to be deaf and there was no vestibular function left. A right homonymou hemianopia was found (fig 2)



2 Case 2 Right homonymous hemianopia after extradural hematoma.

C. Disability

Of the 31 patients examined, 5 were completely incapacitated and 4 moderately disabled Three other patients showed slight memory impairment and lack of concentration, one of them was under anti-epileptic medication because of psychomotor seizures.

Discussion

There were three patients with normal otoneurologic findings, but these showed abnormal findings on eye examination. Nine patients, however revealed no opthalmologic abnormalities, but did show pathologic signs in the otoneurologic tests.

The results of this study confirm the above conclusions of Troupp et al. (1964) in a series of 17 patients.

Despite the manifold signs found in our series, only 5 patients (6%) were totally disabled. This figure accords exactly with the results of Josephson (1962) 4 patients out of 25 were unfit for work due to the injury The number of disabled patients in the series of McKissock et al. (1960) was somewhat higher 8 out of 91 or 8%

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AUDIOMETRIC AND ELECTRONYSTAGMOGRAPHIC STUDIES OF PATIENTS WITH TRAUMATIC SKULL INJURIES

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All the patients with traumatic skull injuries treated in the department of surgery University of Turku, during half a year 1965—66 have been examined for possible changes in hearing and vestibular functions.

The methods of hearing examination were pure tone audiograms, speech audiometry recruitment tests (Fowler' binaural or Reger' monaural methods) and per stimulatory adaptation test. The spontaneous and positional nystagmus have been examined with electronystagmography.

The changes in hearing and vestibular functions have been compared with the various stages of the skull injury.

In road accident patients there very often appears functional disturbances both in the auditory and vestibular organ, if the head has been injured.

On all the skull injury patients treated at the Surgical Department of the University Hospital in Turku who were more than 15 years of age and survived the accident, an otological examination was carried out. The material was collected for half a year in 1965—66. The methods of examination were ordinary ORL examination, audiological examination and testing of nystagmus by means of ENG.

A caloric test could not be performed owing to the risk of infection.

The examination was not carried out until the state of the patient had improved so much that the cooperability could be satisfactory. That could take several days, and therefore it may be possible that some of those who temporarily suffered from a loss of hearing had recovered before the examination.

All the examined were victims of road accidents. In Table 1 the occurrence of the most important injuries are presented.

TABLE 1

MATERIAL AND DIAGNOSIS

Commotio cerebri	35	
Contusio cerebri	6	11
Fr. cranii	11	
Fr. baseos cranii	2	
Fr. pyramidis oss. temporalis	3	10
Skull fractures	23	41
Multiple injuries	6	
Main skull injury	35	41

According to the findings in otoscopy and audiometry the changes in the sense of hearing were classified as follows:

TABLE 2

HEARING RESULTS

Normal hearing		11
Hearing loss caused by skull injury		22
Deaf	(2)	
Dip	(15)	
Abrupt	(1)	
Conductive	(4)	
Other ear pathology		8
	Total	41

The table shows the number of those with normal hearing and of those with hearing losses due to skull injury. The latters are subdivided according to the different types of audiograms. In 18 cases there was a cochlear loss, and in 4 cases a conductive one due to rupture of the tympanic membrane and to bleeding into the middle ear.

The last group, other ear pathology, consists of cases with chronic otitis, occupational deafness and other reasons for the hearing loss than the accident.

A control examination was carried out 3 months later. 19 patients from those 22 with hearing losses came to this study. In 11 cases the hearing had clearly improved and in some it was even normal. In 8 cases the hearing loss was unaltered.

In Table 3 the cases are classified according to the severity of the skull injury. There seems to be no correlation between the lasting time of unconsciousness and the hearing loss.

TABLE 3

HEARING IMPAIRMENT IN DIFFERENT GROUPS — SEVERITY OF THE SKULL INJURY

length of unconsciousness	hearing loss	normal	total
<10 min	13	6	19
10 min—1 h	7	4	11
>1 h	2	1	3
			33

Table 4 shows the hearing results in cases with skull fractures. As can be expected there are also cases of fractures with normal hearing. In all those 3 cases with basal fractures the hearing was impaired. Except of the 2 cases, in which the ear became deaf, the hearing loss was of slight or moderate degree. The threshold for speech was normal and no loss of discrimination was found in speech audiometry.

In adaptation tests only one patient had in the first examination an excessive threshold tone decay, which later at the control examination was found normal. In those who were subjected to Fowler's or Reger's test the balancing of hearing was almost complete.

TABLE 4

HEARING IMPAIRMENT AND SKULL FRACTURES

	normal hearing	hearing loss due to skull injury	(other ear) pathology
Fr cranii	4	5	(2)
Fr baseos cranii	—	1	(1)
Fr pyramidis ossis temporalis	—	2	(1)

In vestibular examinations 8 patients out of 41 (about 20 per cent) showed nystagmus by means of Frenzel's glasses with electronystagmography With the closed eyes, however nystagmus was registered in 14 cases of 22 (about 63 per cent) The elimination of the eye fixation, thus, seems to be important.

Table 5 shows a comparison of different types of nystagmus in patients with hearing disturbances and with normal hearing

TABLE 5

DIFFERENT TYPES O NYSTAGMUS BY THOSE WITH NORMAL HEARING AND WITH HEARING IMPAIRMENT

Type of nystagmus	normal hearing	hearing impairment
Spontaneous nystagmus	1	2
Positional, Nylén I	—	3
Positional, Nylén II	4	4
Positional, Nylén III	—	—
None	3	5
		T tal 22

It appears from the table that injured hearing does not necessarily include vestibular disturbance. Nor does a subjective feeling of dizziness always include any nystagmus that can be registered. On the contrary nystagmus was always combined with a subjective feeling of vertigo wherefore it can be assumed that a registered nystagmus really has been caused by the skull injury Further it is ascertained that nystagmus does not always depend on the duration of the uncon sciousness or the skull fracture In other words it does not correlate with the degree of severity of the skull injury In this respect the findings are similar to those at hearing disturbances. The most common type of positional nystagmus was direction determined (Nylén's type II)

In our material it was noticed that nystagmus, from the point of view of the hearing injury beated towards the opposite side, i.e. towards the healthy ear There was one exception, however a hemotympanum case in which the direction of nystagmus was towards the injured ear As the patient's hearing later on became normal, it may be that nystagmus in this case was due to a temporary irritation caused by hemotympanum

In conclusion it can be ascertained that every second skull injury patient also gets hearing injury which, however in the majority of them is temporary and does not invalidate in any higher degree. Only every third patient noticed

himself that his hearing was damaged. In those cases the disturbances were greater two cases of deafness and four hemotympanum cases. In all the last mentioned the hearing became normal again within three months.

Also vestibular disturbances, which always were connected with subjective feeling of vertigo, appeared rather numerously in more than 60 per cent.

A hearing disturbance does not always presume a disturbance in the vestibular organ or vice versa. The vestibular disturbance can be independent of the hearing impairment.

Although our material is small, it all the same gives clear lines of direction concerning how common the hearing changes and vestibular disturbances are in connection with skull injuries. To observe them without special apparatus (audiometry ENG) is possible, however only in a few cases.

It is very important to do a carefull otoneurological examination, including audiometry and electronystagmography for all these patients as soon as possible. This can be of great value for instance for later insurance treatments.

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DISCUSSION

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Vertigo is rather common finding after head injuries. Typically the complaints start week or more after the trauma, being exaggerated by head movements. The nystagmus can be of the so called *paroxysmal type* i.e. an outburst during a limited period in one or several critical positions. In recent study on 80 patients with paroxysmal positional nystagmus (Stahle & Terins 1965), the reason was head trauma in 18 cases.

Four variants of paroxysmal positional nystagmus have been noted in an electronystagmographic study

1 Type *Dix Hallpike* where the paroxysm occurs in *one* lateral position and is directed towards the undermost ear regardless of whether the position has been assumed strictly according t Dix and Hallpike or by turning over from the supine position. Sitting up is usually accompanied by slight vertigo and nystagmus in th reverse direction.

2. *Type Stenger* which resembles th above b t occurs in rapid changes of position in the sagittal plane especially from the seated t the supine position with head hanging straight down.

3. *Divergent Type* which is characterized by paroxysms of vertigo and nystagmus *in both side positions* after turning from the supine position. In both lateral positions the nystagmus beats towards the floor i.e. diverging away from the central supine position.

4 *Convergent Type* where paroxysmal nystagmus beating upwards from the floor can be provoked in one or both side positions or in the head-hanging positions with th head turned t either side. The nystagmus thus beats towards the central supin position, whence the designatio convergent.

All four types of paroxysmal nystagmus have been found after head injuries, most frequently however the divergent type. In our pinion the symptom probably indicates an otolithic lesion (dislocation or nerve cell lesion) caused by violent linear acceleration and deceleration.

In most patients the complaints disappear spontaneously sooner or later Appropriate physical exercise may be helpful in longstanding cases.

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SYMPATHO-ADRENOMEDULLARY ACTIVITY DURING EXPERIMENTALLY PROVOKED MENTAL STRESS IN PATIENTS WITH LABYRINTHINE DEFECTS

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The effect of psychological stimuli on sympatho-adrenomedullary activity as reflected in the urinary excretion of catecholamines was studied in 10 volunteers with normal labyrinthine function, and in 20 Menière patients with single or bilateral labyrinthine defects. In the normal subjects, experimentally induced emotional stress was accompanied by a significantly increased excretion of urinary catecholamines. This was not the case in the patients with unilateral labyrinthine dysfunction, their adrenaline excretion declined throughout the experiment. In three patients with bilateral labyrinthine destruction the adrenaline excretion remained very low throughout the experiment, and the emotional stress was not accompanied by the rise found in the healthy subjects.

The biological concept of »stress» was put forward about thirty years ago by the Canadian researcher Hans Selye. By stress, Selye denotes the common denominators of the organism's adaptive-protective reactions to any and every kind of influence. In several — perhaps most — cases, the stress reactions are both purposeful and adequate. In other cases, however, they may be too strong, too weak or qualitatively inadequate, and when this happens they can constitute a greater danger to the organism than the stressor which provoked them. It follows that stress has definite medical implications.

Stress occasions a profound transformation of physiological and biochemical processes. This transformation is regulated by impulses from the hypothalamus via the sympathetic nervous system to the adrenal medulla, from which adrenaline is excreted in increased quantities. The increased adrenaline excretion, coupled with a direct stimulus from the hypothalamus, causes the hypophysis to increase its release of ACTH and other hormones. All this has repercussions on the functioning of various systems and organs, as well as at cell level.

Can stress be measured?

Stress can arise from physical as well as mental causes and has both psychological and physiological manifestations. Increasing attention has been devoted in recent years to the *relationships* between the mental and physical processes associated with stress. One of the methods employed in this kind of stress research has been to provoke stress in human subjects and then make simultaneous recordings of mental and physiological processes. The physiological functions most frequently studied include the pulse, blood pressure, muscle tone, galvanic skin response and respiratory movements. These functions have also been used as indicators of the

organism s state of stress, chiefly because they have been found to correlate with the individual s own estimate of his psychic reactions and also because they are assumed to reflect sympatho-adrenomedullary activity It is obvious, in the light of what has already been said that this activity including as it does the release of adrenaline from the adrenal medulla and noradrenaline mainly from the sympathetic nervous system, is a very important link in the functional chain of stress.

It is only in the past decade however that practicable methods have been evolved for making reliable determinations not only of the indirect measures of sympatho-adrenomedullary activity mentioned above but of the adrenaline and noradrenaline contents of various body fluids and tissues. The analytical methods devised by the discoverer of noradrenaline Ulf S von Euler have been of fundamental importance in this respect (Euler & Hellner 1953, Euler & Lishajko 1961) Working on the basis of the central role played by adrenaline and nor adrenaline in the provocation and course of stress reactions, and following a series of experiments (Euler & Lundberg, 1954, Euler et al., 1959 Levi, 1967 Frankenhaeuser 1967) Euler has further suggested that the urinary excretion of these hormones — which roughly corresponds to their release in the organism — may serve as a measure of the intensity of the stress prevailing during the period when the urine accumulated (Euler 1964 1965)

Experimentally induced stress

In the series of experiments which one of us (L. L.) has been conducting since the end of the 1950 s at the Laboratory for Clinical Stress Research shared by the medical and psychiatric departments of Karolinska sjukhuset Stockholm the stimuli used have been simulated situations from working life such as office and workshop jobs, flying in a link-trainer shooting in simulated ground warfare as well as genuine working situations. In the real-life situations, certain details such as the volume of work, the payments system and the background noise were varied experimentally Finally the effects of more specific mental stimuli have been studied, by showing films programmes with a highly varied emotional content to different experimental groups. In all these situations, the parameters studied have included *both* the individual s subjective, self-assessed reactions *and* the objective physiological and chemical changes undergone by the organism. This has served to show that a considerable number of biochemical variables are affected during stress, such as the erythrocyte sedimentations rate blood lipids, proteinbound iodine and serum-iron, as well as the urinary excretion of the stress hormones of the adrenal medulla (Levi, 1967)

Stress and vestibular function

These and similar results — our own and those of others — strongly suggest that those bodily functions which concern the ear nose and throat specialist as well are likely to be affected by and perhaps themselves have an effect upon the general stress reactions. One example of the last-mentioned form of influence is thought to occur in Meniere s disease which is accompanied by considerable, vegetatively

mediated reactions in other parts of the organism. Back in 1953, Fowler & Zeckel reported anomalous reactions in the sympathetic nervous system of a patient suffering from Menière's disease. More than ten years earlier Angyal & Blackman and Angyal & Sherman had observed impaired vestibular function in patients with mental disturbances of the schizophrenic type. Subsequently Bender & Helme (1953) and Pollack & Krieger (1958) have made similar findings in schizophrenic children.

Colehour & Graybiel reported quite recently (1964) that deaf patients with bilateral labyrinthine damage (L-D) after meningitis, failed to display either anticipatory or situational anxiety or the increased urinary excretion of adrenal stress hormones which are seen in healthy subjects exposed to the strains of advanced flying. In their discussion of this result, the authors maintained that »the vestibular organs must be taken into account in evaluating the effect of actual and simulated flight stresses where the gravitational inertial force environment is a variable».

In a subsequent report, Colehour (1964) states that whereas increased corticosteroid excretion rates were found in 21 normal subjects exposed to repetetive twenty-second intervals of (1) zero gravity or (2) zero gravity plus Coriolis acceleration in parabolic flight, there were no reactions of that type in four similarly exposed L-D subjects. This difference in urinary output of stress hormones is proposed to be due to the fact that the L-D subjects did not become nauseated by either experimental situation and were thus not distressed as were the normal subjects. One year later the same author (Colehour 1965) reported similar results in subjects exposed to the violent pitch and roll of a relatively small wooden-hulled boat, which entered a storm described by the skipper as one of the worst he had ever experienced. In spite of the very considerable stressors involved in this situation, the eight L-D subjects exposed to it did not increase their adrenal cortical and medullary hormone excretion.

These results are surprising, because there is good reason to assume that at least the advanced flying must have occasioned other strains apart from those directly connected with »the gravitational inertial forces», at least in the case of subjects who are not used to flying. Thus, Euler & Lundberg had demonstrated in 1954 that flying of a perfectly ordinary kind (troop transports) led to a very considerable increase in the urinary excretion of adrenaline, which they attributed to the mental tension evoked by the flight. Although experimental evidence is lacking, one may expect the storm experience to act in a similar way. Could it be then that Colehour & Graybiel's subjects (possibly for reasons connected with their ear injuries) were *generally* hyporeactive as regards the emotional and/or the adrenal response to various stressors? Is it possible that the labyrinthine organs serve as a link in the stress-conveying neuroendocrine chain of functions and that damage to the labyrinth modifies its action?

We therefore decided to investigate whether patients with labyrinthine dysfunction exhibit a sympatho-adrenomedullary and/or emotional reaction different from that of healthy subjects even when subjected to stressors having no connection with gravitational force, e.g. purely emotional ones.

Catecholamine excretion in healthy subjects during emotional stress

Previous series of experiments (Levi, 1965, 1967) had demonstrated the possibility of using different types of film programme to raise and lower the urinary excretion of adrenaline in healthy female subjects according to the degree of emotional arousal reported by the subjects in their questionnaires. The investigation proceeded as follows:

Twenty healthy female office clerks (age range 17—45, mean 26 years) were shown six different types of motion pictures lasting 90—105 min. each (one programme per evening). Each of these filmshows was preceded and followed by a 90 min. control period. During the control periods the subjects relaxed, reading magazines and listening to soft music. They were not allowed to communicate with each other during the film or the control periods, until they had completed questionnaires. Not until a few minutes before the beginning of each programme were they told what type of film would be shown.

Some of the emotional and endocrine responses to the different film programmes were simultaneously studied. Subjective feelings were mapped out with the aid of questionnaires. Mean questionnaire scores were tabulated as follows: extremely (agitated etc.) 5 points; very 4; fairly 3, slightly 2; not at all, 1. Urine samples were analysed fluorimetrically for adrenaline and noradrenaline. All details in the experimental setting were strictly standardized, including instructions, stimuli, posture, time of day, food and fluid intake, questionnaires, and urine collections. The use of alcoholic or caffeine-containing beverages, tobacco, and any kind of drug was strictly forbidden.

The most powerful emotional reactions, as reported by the subjects, and the most pronounced increases in the urinary excretion of adrenaline, occurred during the fourth of these six experiments. Nineteen of the subjects participated in this experiment.

The main film on this day was Mario Bava's gruesome ghost story »The Devil's Mask« (90 min.) during which the subjects screamed with fear and reported anxiety and dread. The concomitant adrenaline and noradrenaline excretions rose markedly and significantly.

After the end of the second control period on this day, a short film was unexpectedly shown, Robert Enrico's highly dramatic and thrilling »An Occurrence at Owl Creek Bridge« (27 min.). Again, the subjects reported feelings of apprehensiveness. The catecholamine excretion rose, but not significantly so.

This, then, was the reaction of healthy subjects. What about the mental and physiological reactions of patients with labyrinthine defects?

Material and methods

Our subjects this time were twenty Menière patients with single or bilateral labyrinthine defects. Twelve of them had been operated on with resection of the vestibular nerve (Fluur & Toyi, 1965), while five were suffering from Menière's disease at the time and were on the waiting list for surgery. The other three patients had previously suffered from Menière's disease and had bilateral destruction of

the labyrinths following streptomycine treatment (Gejrot 1963). The total group comprised twelve females and eight males. Their ages varied between 23 and 59 years, mean 32 years.

Since the previously mentioned »healthy» control group failed, despite definite emotional reaction, to evince any statistically significant rise in the urinary excretion of catecholamines during the short film »An Occurrence at Owl Creek Bridge», probably owing to the brief period of urine accumulation, this film was combined with the long film »The Devil's Mask» to make a continuous programme lasting two hours. The control periods before and after the film show were also extended to two hours each. Otherwise, however, the experimental conditions were exactly the same as for the control group, the subjects being provided with the same food and drink, the same instructions etc.

Results

A detailed account of the experiment will be given in a future report. However some of the main results may be summarized as follows.

1. *Adrenaline excretion.* Whereas the healthy subjects in the experiment reviewed above had shown statistically significant increases in adrenaline excretion during the film period as compared with the mean of the two control periods, the *unilaterally* labyrinthine defective subjects evinced no such increase; instead, there was a significant decline throughout the experiment (Fig. 1) in keeping with the ordinary circadian rhythm (Leanderson & Levi, 1967).

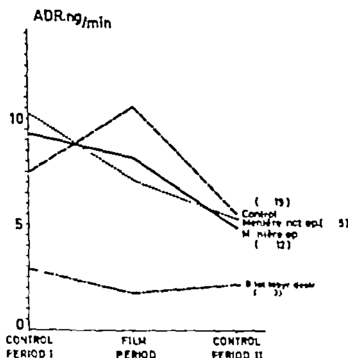


Fig. 1. Urinary excretion of adrenaline (ADR) before, during, and after an anxiety provoking film programme in healthy subjects and in patients with vestibular dysfunction.

The subgroup of the three patients with *bilateral* labyrinthine injury were found to deviate still more from the pattern of the control group with very low adrenaline values throughout the experiment (fig 1).

The mean excretion level during the film period as well as the mean change in excretion between this period and the mean of the two control periods were significantly lower in the 20 L D subjects than in the controls.

2. *Noradrenaline excretion* The film period was accompanied by a significantly increased noradrenaline excretion in the healthy subjects but not in the labyrinthine defective patients, who exhibited a decrease throughout the entire experiment. The excretion levels of the patient group were significantly higher than those of the healthy subjects during the first control period as well as during the film period. Again the subgroup with bilateral labyrinthine injury exhibited excretion levels deviating from the rest of the L-D group (cf. fig 2)

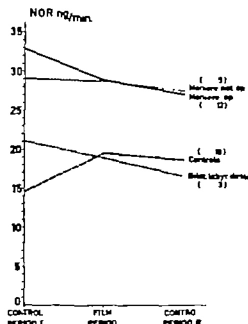


Fig. 2. Urinary excretion of noradrenaline (NOR) before, during, and after an anxiety provoking film programm in healthy subjects and in patients with vestibular dysfunction.

3. *Emotional reactions* The control subjects reported emotional reactions during the film period which were significantly stronger than those of the L-D patients, e.g as regards anxiety and general emotional involvement, whereas the L-D patients reported significantly stronger apprehension during the control periods of the experiment.

Discussion

Thus, our results indicate that in the L D subjects the film period is accompanied by sympatho-adrenomedullary as well as emotional reactions different from those occurring in the control group At present, it can not be said with certainty why this is the case

One possible explanation might have been that the L-D subjects sufferred from impaired hearing as did some of Colehour's and Graybiel's subjects and for this reason did not perceive some of the stimuli included in the film show whereas the normal subjects did. However in order to avoid this source of error our subjects were chosen from among those whose hearing was demonstrated to be normal or next to normal.

Another possibility would be that the patients and the healthy controls participated in this experiment for different reasons which in turn might have affected their attitudes and thereby their reactions to the stressors presented. It is, however unlikely that this should have modified the sympathoadrenomedullary reactions to such a degree as entirely to extinguish the reactions known to occur in healthy subjects. In addition, the film period was accompanied by a significant increase in the level of self rated excitement not only in the healthy controls but also in the L-D subject. In spite of this no deviation from the steady catecholamine excretion decrease throughout the experiment probably due to circadian rhythm was induced by the film.

A third explanation would be that the L-D subjects were generally hyporeactive or had a lower level of sympatho-adrenomedullary activity. It may be recalled that sympathomimetic and parasympatholytic drugs are often used therapeutically in cases of motion sickness and also Menière's disease. It can not be excluded that the low catecholamine output and reactivity is a reflection of an autonomic imbalance associated with these defects in labyrinthine function.

We therefore conclude that our result corroborates the observation made by Colehour & Graybiel that patients with bilateral labyrinthine damage react to stress-producing stimuli in a different way from normal individuals.

The question now arises as to the way in which the labyrinth, and possibly its central relays, serves as a link in the stress-conveying neuro-endocrine chain of functions. This is to be the subject of future experiments.

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EXPERIMENTAL INOCULATION OF GUINEA PIG'S MIDDLE EAR WITH RESPIRATORY SYNCYTIAL VIRUS

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A short report is given of experimental inoculation of respiratory syncytial virus into middle ears of guinea pigs. The virus was isolated from the middle ear cleft 7 days after inoculation in 41 per cent of the inoculated ears. Slight inflammation was detected in most of the infected ears. In evaluating the results, reproduction of virus in the middle ear cl It is considered probabl

An isolation of respiratory syncytial (RS) virus from middle ear exudate of infants was reported by Berglund, Salmivalli and Toivanen (1966). Signs of middle ear inflammation have been reported in earlier studies of infections associated with RS virus (Kapikian et al. 1961, Reilly et al. 1961). The inflammation of human middle ear associated with RS virus infection seems to be very mild. Only a careful examination revealed the presence of middle ear disease in several patients (Berglund et al. 1966). The age of patients, all infants, may be partly responsible for the paucity of the symptoms, but also the inflammatory signs were scanty as a rule. As the guinea pig is known to be susceptible to RS virus (Coates and Chanock 1962) this study was undertaken to investigate whether this virus is capable of producing experimental middle ear inflammation in this animal.

METHOD AND MATERIAL

Virus strains. Two strains, the Randall strain and a strain called Lamminpää were used in the experiments. The latter strain was isolated from a human middle ear by Berglund et al. (1966). The virus was propagated in human amnion cell culture (U-cells) maintained in modified minimum essential medium (Berglund et al. 1966). The infecting dose varied in different experiments from $10^{1.5}$ TCD_{50} to $10^{3.8}$ TCD_{50}.

Control animals were inoculated with either sterile maintenance medium taken from cell cultures, or emulsions of freshly isolated bacterial cultures. The animals were young guinea pigs of the same strain with a mean weight of 230 g.

The inoculation was performed through the drum using Lahikainen's (1953) bayonette needle. The volume inoculated was about 0.1 ml.

The animals were killed by heart puncture and air injection 5, 7 or 14 days after the inoculation. The tissues on the bone around and above the external meatus were aseptically dissected away and a hole was drilled into the posterior recess of the middle ear cleft. The mucosa of the posterior recess was opened

aseptically and samples were taken for isolation of viruses and bacteria. A platinum loop smear was used to take the bacterial samples that were immediately cultured. Smears, mucosal pieces and/or irrigation cultures were taken for virus isolation. After sampling the temporal bone was dissected and immersed in fixing fluid.

Histologic technique. After fixation in 10 per cent formalin solution and decalcification, the temporal bones were cut in slides 6 microns thick at several planes to obtain information from different parts of the middle ear bulla. Haematoxylin-van Gieson and haematoxylin-eosin stainings were used. Only the general types of inflammation, mainly their presence or absence, are recorded in this paper.

RESULTS

The appearance of drum was inspected before inoculation. This was sometimes difficult owing to the narrow meatus and cerumen and required manipulations. *Although the drum often looked normal, many of the animals were* apparently suffering from chronic middle ear inflammation. This was revealed by the appearance of posterior and anterior recesses, by bacterial cultivation and by histologic examination after sacrification. The fact that guinea pigs often suffer from spontaneous middle ear inflammation has been noted earlier (Siirala and Kortekangas, 1954).

In the following evaluation, only ears apparently free of chronic inflammation are considered. Table 1 gives the results of all inoculated ears excluding ears with bacterial inflammation.

TABLE 1

ISOLATION OF RS VIRUS FROM INOCULATED EARS. EARS WITH BACTERIAL INFLAMMATION ARE DISREGARDED

Incubation period in days	RS virus strain Randall		RS virus strain Lamminpää	
	No. of ears inoculated	No. of ears from which virus was isolated	No. of ears inoculated	No. of ears from which virus was isolated
5	1	0	2	1
7	15	6	14	6
14	8	0	0	

The Randall strain was isolated from 6 of 16 ears inoculated 7 or 5 days before the sampling. The corresponding figure for the Lamminpää strain is 7 of 16. The results of Table 1 show that all trials to isolate virus 14 days after the inoculation were unsuccessful. Althogether 17 animals i.e. 34 ears (including also the ears with chronic bacterial inflammation) were inoculated simultaneously with the same virus culture. Nine animals of this series were sacrificed one week after inoculation, virus was recovered from 5 of the 18 ears of these animals, from both ears of one animal. The remaining eight animals were sacrificed two weeks after inoculation, no virus could be detected from their 16 ears using exactly the same methods of isolation.

EXPERIMENTAL INOCULATION OF GUINEA PIG'S MIDDLE EAR WITH RESPIRATORY SYNCYTIAL VIRUS

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Control animals were inoculated with either sterile maintenance medium taken from cell cultures, or emulsions of freshly isolated bacterial cultures. The animals were young guinea pigs of the same strain with a mean weight of 286 g.

The inoculation was performed through the drum using Lahikainen's (1953) bayonette needle. The volume inoculated was about 0.1 ml.

The animals were killed by heart puncture and air injection 3, 7 or 14 days after the inoculation. The tissues on the bone around and above the external meatus were aseptically dissected away and a hole was drilled into the posterior recess of the middle ear cleft. The mucosa of the posterior recess was opened

The detailed methods, results and a discussion will be published elsewhere (Berglund Kortekangas and Laurén 1966)

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ELECTRIC ANALYSIS OF THE ROMBERG TEST

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Two electric scales, based on Strain gauge technique, have been used for objective recording of postural reflexes. The deviation in lateral as well as the leanings in anterio-posterior direction with closed and open eyes have been studied. Normal subjects seem to deviate with an energy about 6–[illegible] of their body weight in the lateral direction and about double as much in the anterio-posterior direction. With closed eyes normals seem to lean more forward than with open eyes. An integration of the deviation from the individual position of equilibrium is suggested as an adequate measure for postural adequacy.

The Romberg test was introduced in 1846 as a tool in neurologic diagnosis. It has still a current importance. An otoneurologist as well as a neurologist still uses this test in his routine work. Many authors have in several different ways tried to objectivize the test. Also electric methods have been employed. A few of these trends will be mentioned here.

Thomas and Whitney (1959) studied with and elegant electric method the anterio-posterior movements of the centre of foot pressure during normal standing in man. Further, also electro-myographic studies have been used to elucidate postural mechanisms (Jansson and Steen 19[illegible], Joseph 1960). The aim of the present paper will be to describe a simple technique for analysis of the Romberg test.

METHODS

Two electric, commercially available scales (the Bofors Co., Sweden) using strain gauge principles were used (fig. 1). A voltage proportional to the weight on each scale was exploited. The difference in voltage between the scales, also expressing the difference in load on the scales, was recorded on one of the four channels of an inkwriter. The amplification was thus adjusted, that 100 per cent body weight of each test subject on one of the scales would give the same deviation of the tracing. The potential difference recorded on the first channel will then, with the test subject placed with one foot on each scale, express in per cent of body weight as a function of time the difference in pressure exerted by the right and the left foot.

The algebraic values for deviations [the deviation towards the right minus the deviation towards the left (R—L)] were electrically integrated and recorded in channel 2. This integration will be referred to as the difference (of deviation). The absolute values of these deviations (R+L) were also integrated and recorded in channel 3. This integration will be referred to as the sum (of deviation). (See fig. 2).



Fig. 1 Normal subject during test in the anterio-posterior direction.

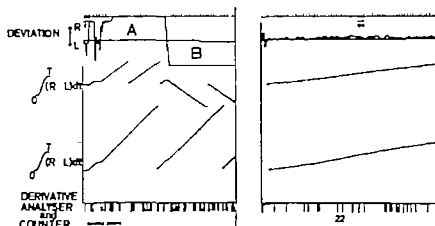


Fig. 2 An objectiv postural test. Left part is calibration, t A all weight of the test person is put on the right foot and t B on the left foot. In the right part is performed Romberg test for one minute. Upper curve The potential difference between right and left scale Second curve A recording of an integration of the difference in load between right and left foot. Third curve A recording of the integrated sums of ll deviations independant of direction. Bottom curve A recording of the mber f rapid distrib tions of weight between right and left foot.

With the test subject in the transverse direction with the anterior part of the feet on one of the scales (the right) and the heels on the other (the left) the examination was continued. The algebraic values for leaning forwards minus backwards (F–B)/ were electrically integrated and recorded in channel 2. This integration will be referred to as the difference (of leaning). The absolute values of these leanings (F+B) were also integrated and recorded in channel 3. This integration will be referred to as the sum (of leanings).

PROCEDURE OF THE TEST

The test subjects were examined both with closed and with open eyes in the lateral direction (standing with each foot on the centre of each scale) and in the transverse direction (with the anterior part of the feet on one of the scales and the heels on the other). The tests were repeated once.

RESULTS

I. DEVIATIONS IN LATERAL DIRECTIONS

A. *Deviations towards the right minus deviations towards the left* $\left[\int_0^T (R-L)\,dt\right]$

In fig. 3 are presented the differences of deviation of the 20 test persons standing

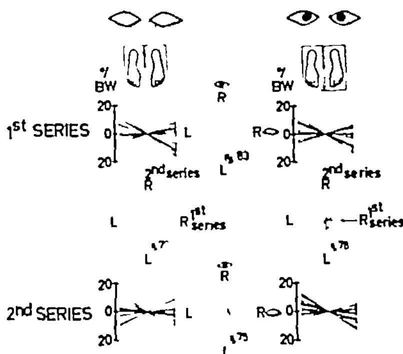


Fig. 3. Average deviation in lateral direction. Values were calculated in per cent of body weight by integration of the difference between deviation towards the right and left during periods of one minute with closed and open eyes and in repeated experiments. The correlations between the four different kinds of experiment are presented as diagrams of deviations with open eyes as a function of those with closed eyes, resp. the deviations in the repeated test as a function of those of the first test. Twenty test subjects were examined.

TABLE I

[illegible] ABSO[illegible] [illegible]LUES [illegible] INTE[illegible]TED DIFFERENCES [illegible]ND SUMS [illegible] DEVI[illegible] [illegible] IN LATER[illegible] DIRECT[illegible] AS WELL AS [illegible] [illegible]NGS [illegible] TH[illegible] FORWARD-[illegible]CKWARDS DIRECTION

	1st series				2nd series			
	lateral		ant.-post.		lateral		ant.-post.	
Eyes	cl	op	cl	op	cl	op	l	op
Average integrated differences [illegible] deviations resp. leani[illegible] [illegible] body w[illegible]ght (R L) resp. (F B)	7.2	6.0	11	13	5.8	5.5	1	15
Averag[illegible] integrated sums [illegible] deviations resp. lean-ings of body weight (R+L) resp. (F+B)	7 7	6.4	13	13	6.7	5.5	11	17
Correlation between integrated differences [illegible]nd sums.	0.90	0.86	0.9[illegible]	0.85	0.81	0.70	0.91	0.88

TABLE II

[illegible] DI[illegible]FERENCES, TESTED BY [illegible] TEST [illegible]ETWEEN DIFFERENCES [illegible] DEVI[illegible] [illegible] RESP. LEANING IN 1ST [illegible]ND 2ND SERIES, RESP. CLOSED [illegible]ND [illegible]PEN EYES. LEVEL [illegible] SIGNIFIC[illegible] [illegible] 5%

	1st–2nd series of $\int_0^T$ (R L) dt		1st–2nd series of $\int_0^T$ (F B) dt	
Closed eyes	12+ 8−	not s.	13+ 7−	not s.
Open eyes	7+ 11−	not s.	9+ 6−	not s.
	Closed–Open eyes of $\int_0^T$ (R L) dt		Closed–Open eyes of $\int_0^T$ (F B) dt	
1st series	13+ 5−	not s.	14+ 4−	s.
2 nd series	12+ 7−	not s.	17+ 3−	s.

with closed resp. open eyes, and at repetition of these tests. From table I and from fig. 3 can be derived, that normals, when standing upright, put as much as 15 % (averagely 6 [illegible]) of their body weights, more on one foot than on the other. Table II shows that there is no significant mean difference between the four tests. This, together with the high correlations between the different tests of the same individual presented in fig. 3, indicates a good re-test reliability and also a relative independence of visual cues for normal standing.

Further, a statistical analysis of the differences of deviation indicate that these values are rather equally distributed over the whole range. This means about the same probability to find, in a normal population about 15 [illegible] deviation towards the right or the left as to find no deviation at all (table III).

B. *Deviations towards the left plus deviations towards the right.* $\int_0^T (R+L\,dt)$

The values for average differences and average sums of deviation are about the same (table I). This together with the sign test, presented in table IV, indicates

TABLE III

[illegible] OF DEVI[illegible] ... EXPECTED ... EMPIRIC[illegible] ... [illegible] ... EXPECTED ... CALCULATED ... [illegible] DISTRIBUTION ... EXPECTED A[ND] EMPIRIC[AL] ... DEGREE[S] OF FREEDOM

Inter[illegible]		I	II	III	X	Probability und[er] null hypothes[is]
Closed [e]yes 1st series	[illegible] Imp.	6	6 7 [illegible]	6.	0 1	p>[illegible]
Open eyes 1st series	[illegible] Imp.	6 5	[illegible] 7 8	[illegible] 7 7	0 7	p>0.2[illegible]
Closed eyes 2nd series	[illegible] Imp.	6.	6,7 9	6 7 6	1.3	p>0.[illegible]
Open eyes 2nd series	[illegible] Imp.	6. 7	6,7	[illegible] 7 6	[illegible]	p>0 [illegible]

TABLE IV

[illegible] ... DEVI[ATIONS] ... 5

	$\int_0^T (R-L)\,dt$	$\int_0^T (R-L)\,dt$	$\int_0^T (L+R)\,dt - \int_0^T (L+R)\,dt$	
Closed eyes 1st series	6 9	not	3 13	s.
Ope[n] e[y]es 1st series	10	not s.	[illegible] 12 –	not s.
Closed eyes 2nd series	6 10	not s.	6 11	not s.
Open eyes 2nd series	9	not s.	[illegible] 12	not s.

that the differences (R L) and sums (R+L) of deviations are about the same This means that normals tend to keep their amount of deviation towards one side as well as their direction of deviation without much deviation towards the opposite side

II DEVIATIONS IN ANTERIO-POSTERIOR DIRECTION

A. *Deviations forward minus deviations backwards* $\int_0^T (F-B)\,dt$

In fig. 4 are presented the differences of leaning (F B) with open and closed eyes. From a comparison with the result in fig 3 it is quite clear that the leanings in the anterio-posterior direction is much larger than the deviations in the lateral direction Further an analysis of the values indicate a tendency to lean more forward with closed eyes than with open eyes. This was shown by testing for mean difference by the sign test (table II) No significant difference was found at repetition of the tests (tabl II).

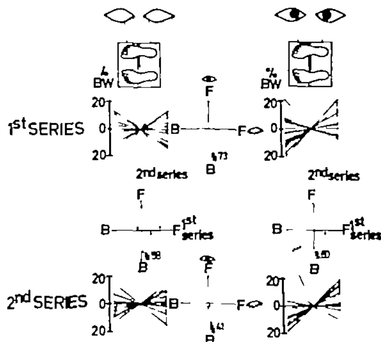


Fig. 4 A verage leaning in terio-posterior direction. Values were calculated in per cent of body weight by integration of the difference between forward and backwards leaning during period f on mi t with closed and open eyes and in repeated experiments. The correlations between the four different kinds of experiment are presented as diagrams f the leanings w th open eyes as f nction f those w th closed eyes resp. th leanings in the repeated tests, as function f those of th first tests. Twenty test subjects were examined.

B *Deviations forward plus deviations backwards* $\left[{}_0\int^T (F+B)\,dt\right]$

The sum of leanings (F+B) was found statistically larger than the difference of leanings (F—B), see table II. This indicates more swaying in the anterio-posterior than in the lateral direction, but also more passing of the base line (equal load on the anterior parts of the feet as on the heels) On the other hand, a close correlation between the sums and differences, presented also in table I means a tendency of the test subject to keep their patterns also in the anterio-posterior direction.

DISCUSSION AND CONCLUSION

Before starting the present investigation, we assumed that a normal subject, standing in erect position would balance himself upright by approximately symmetric deviations from the position with equal load on each foot. This assumption implicated that integration of deviations from symmetric weight distribution between the feet, would give an expression for the precision in the postural system and this was meant to be a quantitative measure for the evaluation of the Romberg test The experiments accounted for here seem, however to prove that normal test persons show a more or less asymmetric weight distribution between their

feet during standing in erect position. Our statistical analysis also indicates that the asymmetric equilibrium positions are more or less evenly distributed over the whole range in a population of normals.

The analysis further shows that in the anterio-posterior direction the leanings from equal loads are larger than in the lateral direction. Also in the anterio-posterior direction each individual seems to prefer a certain distribution of load between the anterior part of the foot and the heel. It is also interesting to note that most persons tend to lean forward when they close their eyes.

As a considerable unequality in load between right and left foot in normal standing thus must be regarded as quite normal, a measure of this unequality can not be an adequate expression for the precision in the postural system. Therefore has been developed a method to measure the total deviation from the deviated position each person employs in his normal standing. Such a recording is presented in fig. 5. It is believed that a total variation by this last integration will furnish a

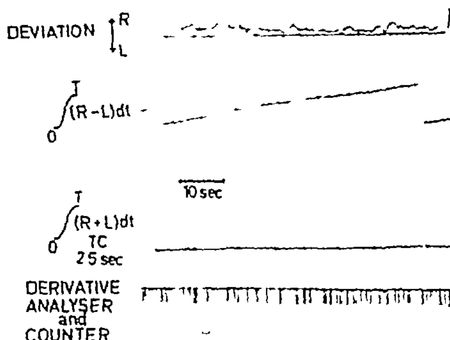


Fig. 5. The same kind of recording as in fig. 2. Here is introduced the integration of the sum of the deviations (time constant of 2.5 sec). In this way is integrated the variations from any deviated position (test person m. y. home)

proper expression for the adequacy of the postural pattern. Experiments with these arrangements are under progress.

STATISTICAL METHODS

The variables studied here were the integrated algebraic differences between load on the right and the left scale resp. absolute values of differences from the zero-line (corresponding to equal load on both scales). The variables studied can not be assumed to be normally distributed in the population studied.

Actually it has been possible to show in the case of lateral deviation, with rather great certainty that the distribution is not normal regarding the algebraically integrated deviations

The variables determined under different conditions have been tested for mean deviations by using the non parametric sign test. Differences between the two variables under the same conditions have been tested with the same method. Correlations have been expressed by Spearman's rank-correlation coefficient

The distribution of the estimated values for algebraically integrated deviations in lateral direction has been studied simply by dividing the range into three intervals of the same measure and counting the frequencies of values in each interval (table III) These frequency values have been tested by the χ^2-method for significant differences from expected values calculated under the assumption of a rectangular distributoin. One degree of freedom was used. A 2.5 level of significance means a good guard against false acceptance of the proposed hypothesis.

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MALIGNANT GRANULOMA

CLINICAL FEATURES, PATHOLOGY AND TREATMENT

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Short historical review. Definition of the disease will be discussed. Diagnosis and histopathological picture will be described.

Histories of about twenty cases which have been treated at the Karolinska Sjukhuset, Stockholm. Radiation and cortisone treatment have given the best results. The prognosis has generally been bad but the disease seems to be delayed to a certain extent by adequate radiotherapy.

History

Just 70 years ago McBride presented a case of rapid destruction of the nose and face in a 20 year old man. During the twenties a number of similar cases were described under various designations, among them osteomyelitis necroticans gangrenous osteomyelitis, granuloma gangraenescens and lethal midline granuloma. The first to describe a condition consisting in a destructive process in the nose associated with diffuse alterations resembling periarthritis nodosa was Klinger (1931). In 1939 Wegener reported 3 cases of what is now known as Wegener's granulomatosis. In the forties several cases were described, among them 3 by Siirala (1946) in Finland, but it was not until the next decade, when cortisone was first used in this disease, that the discussion was pursued further. Friedmann (1955) considered that malignant granuloma in the nose could be divided into two distinct groups: a classical type in which external ulceration of the nose is unaccompanied by general alterations, and a type in which the destruction does not extend superficially and where there is ulceration of the palate, pharynx, etc. and widespread necrotizing angiitis and granulomatosis in the kidneys, spleen, lungs and other organs. Opinions are still divided on whether malignant granuloma in the nasal region is a pathologic entity or a number of distinct diseases with this manifestation. A careful and thorough description of the clinical features of the disease and its possible causes has been published by Mills (1958); he points to the difficulty of distinguishing the local and general forms and states that the evidence points to the disease being a kind of collagenosis, which has developed from a hypersensitivity reaction.

Clinical features

The condition appears more often in men than women and is commoner in early middle age than later on in life. In Mills' series of 80 cases from the literature the commonest age is between 25 and 45 years. In the present series of 16 estab-

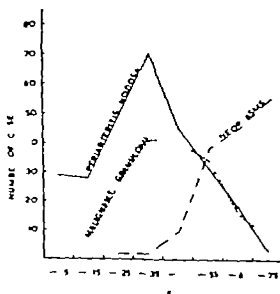


Fig. 1 Age distribution in malignant granuloma compared with periarthritis nodosa nd malignant neoplasm in the asal region. (After C. P. Mills, 1958 Courtesy of J Lary g).

lished cases only 5 are women and the mean age is 45 years. The age distribution is practically the same in the two series (fig 1)

The commonest primary site of the disease is the nasal cavity and the para-sinuses, with the pharynx region and the palate less often affected. The disease commonly originates as recurrent sinusitis, usually unilateral, and in some cases repeated sinus operations have been performed before the diagnosis could be established

Often the first manifestation of the disease is unilateral or bilateral obstruction of the nose with readily bleeding thickened mucosa and serosanguinous discharge As the disease progresses there may be swelling of one side of the nose or cheek and ulcers may appear in the nasal vestibule or at other sites (figs. 2 and 3) some times initially in the palate, alveolar process or pharynx (fig 4). The ulcers or local processes develop fairly rapidly into necrotizing foci with purulent and foul-smelling discharge The usual signs of resistance accompanying an inflamma ion *including fever poor general condition loss of appetite and even leukocytosis are* notably absent. The granulation tissue and necrosis continue to extend, often rapidly to the surrounding cartilage and bone. In some cases extensive and dis-figuring dermal necrosis develops. The patient may develop changes in the kid neys, lungs, spleen and other organs similar to those in periarthritis nodosa. Death usually ensues after a few months or a year or so from sepsis, massive haemorrhage or cachexia or in the case of general alterations, usually from uraemia.

Pathologic picture

In the patho-anatomic examination of the series from the lesions in the upper respiratory tract an inflammatory tissue reaction is observed, the appearance which varies with the age of the processes. The early picture is characterized by a fairly marked serous exudation (fig 5) and the presence of inflamm... ce...



Fig. 2



Fig. 2 and 3. A 17 yea -old girl with maligna t granuloma f the right maxillary sinus with eruption through the palat



Fig. 1 Malignant granuloma in the palat after irradiation and steroid therapy



Fig. 3. During the early stage serous exudation and relativel numerous leukocytes in the loose granulation tissue (Ca. × 200).

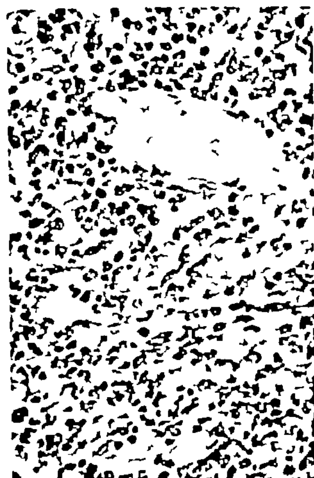


Fig. 6. Richly cellular granulation tissue from the lat[illegible] [illegible]

of both poly- and mononuclear types. There is sometimes moderate eosinophilia. The later more typical alterations, however, are of the proliferative type, the cell flora being dominated by mononuclear cells, chiefly lymphocytes and plasma cells (fig. 6). There is also a tendency for proliferation of fibroblasts and capillary endothelium, giving a general picture of a granulation tissue with no specific characteristics. In addition to the alterations mentioned there will, however, also be a usually quite pronounced tendency for necrotization and vascular damage. The latter consists in an oedematous swelling or fibrinoid necrosis of the wall. Proliferation of the intima and thrombotization are also often seen (fig. 7). The necrosis located in the actual tissue is also fibrinoid in type. It is probably not to be ascribed entirely to infarction due to the obliterating vascular processes.

Causation

Theories on the causation of this obscure disease are innumerable. The pathologic picture is devoid of characteristics but resembles that presented by diverse allergic conditions. In the last few years there has been a tendency to ascribe the disease an allergic basis. A diagnosis of malignant granuloma in the nose is made





Fig. 7 a. Thrombotized vessel whose wall displays thickening oedema and infiltration of cells. (Ca. × 115).

Fig. 7 Densely cellular granulation tissue with extensive fibrinoid necrosis in the upper left part

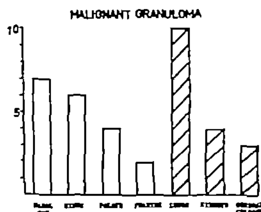


Fig. 8. Distribution of malignant granuloma (white bars) and secondary changes (hatched) according to site.

on the basis of the morbid history and the clinical and histologic findings and, perhaps most important, by a process of elimination of other conditions, such as tuberculosis, neoplasm and fungoid and bacterial infections.

Treatment

The treatment for malignant granuloma has varied enormously and most form have been tried Every conceivable type of antibiotic has been given but without real success. Surgical measures have been tried but the results have often been depressing and in many cases a progress of the alterations has followed Radiotherapy and corticosteroids can retard the disease to some extent but in the case of cortisone large doses are required and the treatment must be introduced at an early stage and continued for a long time It must of course be given under careful control and with simultaneous antibiotic protection

The present series

In the last 15 years 23 cases of malignant granuloma in the nasal region have been recorded at Karolinska Sjukhuset A critical scrutiny of this series disclosed that 4 cases had definitely not had the disease but tumours or non specific infections. In 3 cases there was no reliable pathologic evidence of the disease and the diagnosis was doubtful from the clinical aspect these cases have therefore not been included in this collation Of the remaining 16 cases 10 have been reported earlier and described in detail by Hultberg Moberger and Mårtensson (1957) Cortisone was found to have some effect in retarding the rapid course of the disease and so did radiotherapy in some cases but the prognosis was considered grave It was suspected that the disease might be an allergic manifestation and when staphylococcus aureus was found in most of the cases, as reported by other authors, it was inferred that this might be the cause of the allergy The age and sex distribution of the present series has been touched on above The distribution according to the primary site of the changes is closely consistent with the information in the literature Since only one half of the cases came to autopsy it was difficult to establish any secondary alterations of the disease It was found, however that in no less than 10 cases there was radiologic evidence of alterations in the lungs reminiscent of metastases, tuberculous or non-specific inflammatory infiltrate (fig 8) In 4 cases there were signs of renal impairment consisting in albumin in the urine and red corpuscles in the sediment In 3 of the autopsied cases there were general changes in the liver spleen and other organs A striking feature was the high sedimentation rate which exceeded 50 mm in 9 cases and 25 mm in 13 In 4 out of 5 cases, in which an examination of the blood protein was made there was an elevation of globulins, chiefly of the gamma fraction. The sedimentation rate and the gamma fraction of the serum protein were elevated when the disease was in an active stage and in the 2 cases, in which the course of these parameters was followed as the disease developed the values rose with the formation of granulation tissue and fell when there was a tendency for regression This would seem that the sedimentation rate and the gamma globulin level might provide a measure of the intensity of the disease. In 10 out of 12 cases, in which bacteriologic cultures were performed Staph aureus was found. In one case there was proteus and in another streptococci In some cases the staphylococci grew in

spite of the application of various kinds of antibiotics. In 2 cases repeated attempts were made to isolate viruses but without success.

As regards treatment X-ray therapy was given in 15 cases, usually 2 000—3 000 r Corticosteroids usually prednisolone in a dose ranging from 15 to 50 mg, were given concurrently in 12 cases. As a rule the steroid treatment was given as high doses for a short period or small doses for a longer period. It was frequently observed that a large enough dose secured a marked regression, whereas with inadequate doses there was a deterioration. In one case cytostatic treatment with methotrexate — 7.5 mg daily for 3 weeks — was tried. With concurrent steroid treatment the alterations regressed to some extent but as leukopenia developed the methotrexate was witdrawn, and then there was a rapid spread

The prognosis was usually grave Six cases survived about 6 months, and 6 about 12 months, one of the remainder survived for 1 year and another for 5 years before succumbing to the disease while one patient after 12 years developed a malignant melanoma in the nasal region and mammary carcinoma, from which she died. One patient has been receiving treatment for a year and is at present without symptoms, but is still taking fairly large doses of cortisone. The survival time was evidently unrelated to age or sedimentation rate nor was it definitely related to the irradiation or steroid dose given, the 2 patients surviving for 3 and 5 years received only about 2 500 r and no cortisone The survival would seem not to depend on whether the changes were limited to the upper respiratory tract or were accompanied by others elsewhere in the body

To summarize, the present series consisted largely of men and the age distribution ranged from the teens to senility though with a predominance of middle-aged. The sedimentation rate was high, in a few cases exceeding 100 mm The serum globulin, especially the gamma fraction, was at least moderately elevated, Staph aureus was present in the majority of cases and no virus could be isolated. Radiotherapy and corticosteroids were given, the former usually having a moderate, temporary effect while the latter were possibly more effective though by no means curative It is conceivable that the disease like periarthritis nodosa, can occur in episodes and that with the aid of corticosteroids in particular the pathologic process in the active phase of the disease can be fairly successfully treated Experience of cytostatics in this connection is too limited to permit of any conclusions. The survival time has usually been short, but for some obscure reason 2 cases have lived for several years, while a cure would seem to have been effected in one case, though the patient succumbed to two other malignant diseases. In spite of the numerous cases reported in the literature and the variety of theories that have been advanced the problem of malignant granuloma remains unsolved.

So far as malignant granuloma is concerned, we would seem not to have advanced far from the depressing position in 1921 when Sir Robert Woods declared that the disease is was puzzling to the pathologists as to the clinicians

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OBSERVATIONS ON UNILATERAL BONY SWELLING OF MAXILLA, —FIBROUS DYSPLASIA

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The author has observed 2 cases of unilateral fibrous dysplasia of maxilla during a period of 16 and 7 years respectively. The changes of the bone appeared in the early teens, and seemed to originate in the alveolar process in the region of a solitary and malerupted molar tooth. The bony swelling spread from this tooth and outwards through the maxilla, gradually receding towards the periphery. Certain clinical changes are observed as one of the cases reached mature age.

The opinion is forwarded that fibrous dysplasia of maxilla in these cases may be elicited by the vibratory and mechanical impacts of the displaced tooth to the bone by the act of biting and chewing, as this mechanical stress in cases of malocclusion, represents an abnormal physical irritant to (growing) bone.

The author points to the lack of analysis of dental aspects in most publications on this topic. He also compares the bony changes of fibrous dysplasia with the changes of the otic capsule in cases of otosclerosis, in which instances vibratory forces also seem to play a part.

Two cases of unilateral fibrous dysplasia of maxilla will be presented. They are observed during a period of 16 and 7 years respectively.

Case no. 1 was first seen in 1948 when she was 16 *years old (16, 17, 18).* She had at the age of 14 all her first molars extracted and noticed in the following two years a bony swelling of the *left maxilla*, presented as a thickening of the alveolar process and a bulging of the buccal sulcus from the region of the 2. molar to the canine fossa, and a swelling of the palatal side of the alveolar process as well. Comparing the dental state of the two sides of the maxilla, it was found that the 2. molar on the right side nearly had closed on to the neighbour tooth, the premolar, while on the left side there was a gap between those two teeth about



Fig. 1. Plaster cast of maxilla, 1948. (Case no. 1)

a tooth breadth wide (fig 1) So the 2. molar on the *left side* of the maxilla had become a solitary tooth standing isolated in this quadrant of the jaw and thus taking the full load of the impact and vibration of the biting force which here is at its peak, while the 2. molar on the right side with its closer connection to the premolar had a less vulnerable position

Extraoral radiographs gave a clear picture of these proportions and especially on intraoral films the bone trabeculae had the characteristic »ground glass pattern« X ray examination of the cranial and facial bones showed the swelling to affect the left maxilla only with a smooth and gradual transition to normal bone pattern in the periphery This was most clearly seen on intraoral films, a distinction from tumors which usually have a marked demarcation line

Judged by digital pressure the bone had normal solidity but by elevation of the mucous membrane, which had a normal appearance there was found a very thin cortical layer and a sanguinous spongiosa which had a soft consistency Histology conformed this impression, and the pathology report concluded with the diagnosis, Osteofibroma which lately has been changed to fibrous dysplasia.

This case was again observed 6 years later No obvious external changes was found when plaster casts taken 1948 was compared with casts taken 1951 But on photography the lower margin of the left orbit was found a trifle elevated and the eye slid a little narrower on the left side compared to the right side and the bony swelling in the buccal sulcus was less prominent especially towards the canine fossa where a local prominence on the buccal side of the alveolar process adjacent to the canine tooth was found instead (fig 2) The dental state was unaltered.

After another 10 years, in 1961 this lady was seen again She had married and had got two children Her wisdom teeth had been extracted and the bone pattern



Fig 2. Local bony prominences in buccal sulcus of left maxilla, 1951. (Case no 1)



Fig. 3. Local prominences of bone in buccal sulcus, 1964 (Case no. 1)



Fig. 4. Case no. 2. Swelling of left maxilla and slight elevation of left orbit (as was also found in case no. 1)

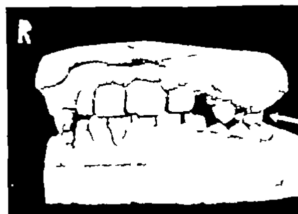


Fig. 5. Plaster casts showing the dental state (1958). Arrow points at the first molar which are standing in crossbite position and are the only molar in occlusion. Prominent swelling of left buccal sulcus.



Fig. 6. I rtly obliteration f left maxill ry sinu



Fig. 7 Occusal radiograph f ma illa howi g the fin meshwork f bone on the left



Fig. 8. Fib osis of the maxillary bone.

on intraoral film showed a tendency to normalize, though radiography of maxilla and sinuses on the left side showed defenite changes from normal. But the bony swelling of the buccal sulcus showed further reduction, as there was now only local prominences of bone over each alveolus of the remaining teeth of the left upper jaw (fig 3). Similar bony swellings can be observed in normal individuals who have teeth standing apart and thus sustaining occlusal trauma (Fig 5a p158)

Case no 2 is a boy who has been observed since 1958, when he was 10 years old (Fig 4). In the previous year when he was 9 he had his deciduous molars pulled out, which was 2 years before normal term. In this case the *1 molar* only was in occlusion at that time and had the whole load of the impact of bite. In addition this molar on the left side was standing in a crossbite malocclusion (Fig 5). This unfortunate position usually has a deteriorating effect as the horizontal component of the biting force is more active. — During the year a swelling occured of the left maxilla, causing a bulging of the buccal sulcus from the region of the 1 molar and forwards to the canine fossa (Fig 5) No change towards the palate was observed. The hard bony swelling was visible also from outside on the cheek, and a slight elevation of the left eye alid was observed. He had otherwise no subjective symptoms, and he had normal Calcium and Phosphorus blood values, which was also found in case no 1

Radiographs of maxilla and nasal sinuses gave a similar picture as in the first case (Fig 6). The left maxilla only was affected and a marked obliteration of the left maxillary sinus was found. A gradual regression towards normal bone structures in the periphery was seen on intra-oral film. The changes showed most markedly in the region of the 1 molar where it seemed to originate and where also the fine meshwork of bony trabeculation was most evenly distributed (Fig 7)

Radiographs of other parts of the body showed normal bone formation.

By elevation of the mucous membrane and chiseling off the bony swelling in the buccal sulcus of the left upper jaw there was found a thin cortical layer which towards the periphery of the bone had a more normal character The spongious bone was soft and highly vascularized and could be cut by a knife or any sharp instrument

Histology showed the picture of fibrous dysplasia (Fig 8).

COMMENTS

In the publications of 1949—58 & —60 on this matter the author suggested that this deformation of the jawbone might be caused by a physical irritant, substantiated by the vibration transmitted to the bone from the traumatic impact on a singular tooth.

When the bony swelling has reached a certain stage, there is created equilibrium between the size and amount of bone formed, and the causative agence, a sort of steady state The bone seems to add in quantity what it lacks in quality and adapts to the new situation by forming a spongy sort of bone, and the general rule that blood supply is raised in tissues exposed to increased function also applies to bone That may explain the rich vascularization of these lesions.

The *histology* of the bone in these cases compared to the bone in cases of *otosclerosis* gives a similar picture of fibrosis and vascularization. It is interesting also to note that in both instances there are movable parts, the tooth and the stapes, connected to the bone by fibrous ligaments. A better understanding of the reaction of bone to physical irritants caused by vibrating forces, might help to solve the problems of etiology in these diseases.

There has been a tendency by some authors to place similar cases of jaw lesions into the tumor group, such as *osteoma fibroosteoma* or *osteofibroma*. Frequently *osteitis fibrosa* was the diagnosis of unclassifiable bone lesions, but lately this »label» has been changed to *fibrous dysplasia* consisting of both monostotic and polyostotic forms.

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SPONTANEOUS COURSE OF 220 PERIPHERAL NON-TRAUMATIC FACIAL PALSIES

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220 patients with acute peripheral, non-traumatic facial palsies were examined. Out of the main group of 181 idiopathic palsies 140 were total and 41 incomplete. The remaining groups were: herpes zoster 12 patients, polyneuritis 8, diabetes 7, pregnancy 4, Melkersson's syndrome 2, and parotic tumor 1.

At the first consultation a routine ENT-examination was made and the extent of the paralysis carefully described. To this was added audiometry, examination of the stapedius reflex, taste threshold, nasolacrimal reflex, and vestibular function. The patients were seen frequently until the paralysis disappeared or reached a stationary stage.

Although no treatment was given except facial exercises all the patients regained complete or partial function, the majority showing the first sign of function within three weeks. A smaller group improved after 2—4 months.

Most patients recovered completely, a few showing varying degrees of sequelae which were rarely cosmetically severe. Generally the risk of incomplete recovery was greater the later the function began to recur.

In 1821 idiopathic facial palsy was described for the first time by Sir Charles Bell. To-day, almost 150 years later, a perusal of the literature reveals that the great majority of cases of peripheral facial palsy must still be considered idiopathic, i.e. of unknown aetiology. And what is more remarkable, there is no really large series to elucidate its spontaneous course. This is no doubt due to the enormous therapeutic activity by methods which have changed in the course of time.

The present study is the result of collaboration between the University E.N.T. and Neurological Departments of Rigshospitalet, Copenhagen. Its object was to show the spontaneous course of non-traumatic peripheral facial palsy, in particular the idiopathic variety. Owing to the limited speaking time the results will be submitted in a schematic way and a number of interesting details will have to be left out.

Method

When the patients were first seen they had a routine otorhinolaryngological examination. The facial palsy was carefully examined and the function of the forehead, eyes, and mouth, including the marginal mandibular branch, accurately recorded. In addition they had audiometry, test of taste by the Boernstein method, tests of stapedial and nasolacrimal reflex, vestibular tests, comprising spontaneous and positional nystagmus, and a caloric Hallpike test. The technique and significance of these tests were described by Kristensen and Zilstorff yesterday morning. Finally the first consultation also included an ordinary neurological examination.

The patients were seen at brief intervals, at the outset once a week, until the palsy had remitted or become stationary All the patients with sequelae have been followed for at least one year

Material

The study comprises the case material for 2 years, a total of 220 including 181 with idiopathic palsy Of these cases 140 were total and 41 incomplete. Seventeen were associated with herpes zoster 8 with polyneuritis, 7 with diabetes mellitus, 4 were pregnancy palsies, 2 had Melkersson s syndrome, and one had a parotid tumour

Results

In this series idiopathic palsy was equally common in males and females and equally common on the right and the left side. There was also no definite seasonal variation during the 2 years of the study The age distribution does not differ significantly from that of the population as a whole. The youngest patient was 3 and the oldest 88 years of age.

Fig. 1A gives the time of incipient remission of the palsies of various aetiological types. It is interesting that in more than 85 ,• of the idiopathic cases function

Cause of palsy		Incipient remission (mo.)								total
		0	/	/₁	/	1	2	3	4	
Idiopath.	incompl.	41	0	0	0	0	0	0	0	41
	total	0	47	49	20	3	3	8	10	140
Herpes zoster		0	0	2	1	0	1	9	4	17
Polyneuritis		1	0	0	0	0	2	2	4	8
Diabetes mell.		4	0	2	1	0	0	1	0	8

Fig. 1A. Time of incipient remission.

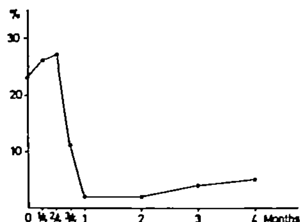


Fig. 1 B Graph representation of the time of incipient rem sion for idiopathic facial palsy (abscissa=months, ordinate % of entII series).

returned within the first 3 weeks Fig. 1B This also applies to 3 out of the 17 patients with herpes zoster It is also interesting to note that in one of the cases with polyneuritis the associated facial palsy was incomplete.

Fig 2 shows the time of full remission or a stationary condition in relation to the time of incipient function for the idiopathic cases. It will be seen that incomplete palsies disappear entirely nearly always in the course of one month. The patients who regain movement during the first two weeks nearly always remit entirely The remission occurs sooner for those who show regression during the first than the *first than the second* week. *When remission does not occur until the third week or* later a significantly greater part of the patients develop sequelae. The proportion of these patients is the greater the later the first movement returns.

Incipient remission (mo.)	Complete remission (mo.)												sequelae (> 1 yr.	total
	/₁	/	1	1 /	1 /	1 /₄	2	3	4	5	6	total		
0	4	17	18	1	0	0	1	0	0	0	0	41	0	41
/	2	16	14	7	1	0	2	2	0	2	0	46	1	47
/	0	1	15	8	4	3	5	7	1	1	0	4	4	49
/	0	0	1	0	0	0	0	2	2	5	2	12	8	20
1	0	0	0	0	0	0	0	0	0	0	0	0	3	3
2	0	0	0	0	0	0	0	0	0	1	0	1	2	3
3	0	0	0	0	0	0	0	0	0	0	1	1	7	8
4	0	0	0	0	0	0	0	0	0	0	0	0	10	10
—	—	—	—	—	—	—	—	—	—	—	—	146	35	181

Fig. 2 Time of complete remission tationary condition for patient with idiopathic facial palsy

A classification of the severity of sequelae is shown in Fig 3 Most emphasis is laid on the residual palsy secondary importance being given to other sequelae such as contraction and associated movements which are by far the most common ones.

Grade of sequelae	Palsy	visibl			eye closes	contraction	associated movements	tic	crocodile tears
		at rest	moderate movements	large movements					
I	negligible	—	—	+	+	—	+	+	—
II	mild	—	+	+	+	—	—	—	—
III	moderat	+	+	+	+	+/—	+/—	+/+	+/—
IV	severe	+	+	+	—	+/(+)	+/(—)	+/(—)	+/—
V	total	+	+	+	—	—	+	—	—

Fig. 3. Classification of the grade of sequ lae

Fig 4 gives the degree of sequelae in relation to the time of incipient remission. It is clearly apparent that the later the palsy starts to remit, the greater is the risk of severe sequelae. 19 / do not regain normal function, but only half these cases, or 9 / of the total series, developed definite sequelae

Incipient remission (mo)	Sequelae (grade)					
	Total	I	II	III	IV	V
/	1	1	0	0	0	0
/	4	3	1	0	0	0
/1	8	8	0	0	0	0
1	3	1	1	1	0	0
2	2	1	0	1	0	0
3	7	2	5	0	0	0
4	10	2	6	2	0	0
Total	35	18	13	4	0	0

Fig 4. Grade of sequelae of the idiopathic palsies related to the time of remission.

In Fig. 5 you see the degree and frequency of sequelae following palsies of various causes. A comparison of the ultimate results for the idiopathic palsies with late remission, in two months or more, with the herpes zoster and polyneuritis groups (Figs. 4 and 5), shows no definite difference. This is highly interesting As is evident, the prognosis is poorest for the diabetics, and this must be due to their polyneuropathy

Diagnosis	Number of palsies	Patients having sequelae					
		total	Grade				
			I	II	III	IV	V
Idiopath.	181	35	18	13	4	0	0
Herpes zoster	17	12	1	5	6	0	0
Polyneuritis	8	7	1	2	4	0	0
Diab. mell.	8	7	1	2	4	0	0
Total	214	61	21	22	18	0	0

Fig. 5. Grade of sequelae in relation t aetiology

The tests of taste by the Boernstein method revealed loss of taste on the anterior two-thirds of the tongue on the side of the palsy in all idiopathic cases whose remission did not start until the 2nd—4th month, and also in all patients with herpes zoster and polyneuritis. The same groups showed abolished stapedial reflex. Among the cases of idiopathic palsy remitting within 3 weeks, taste and stapedial reflex were abolished in the majority while a few had reduced and a very few normal reactions.

The nasolacrimal reflex was found to be reduced in 1 out of 140 with idiopathic total palsy, in 10 out of 17 with herpes zoster and in 4 out of 8 with polyneuritis.

Hearing impairment of the perceptive type was not found in any case.

Vestibular affection was demonstrated in 2 idiopathic cases, in 10 of herpes zoster and in one of polyneuritis.

Concluding remarks

As you have seen from the figures, nearly all the patients (76 %) with idiopathic palsy began to regain their function during the first 2 weeks, which indicates that the nerve has been blocked, or after the second month, indicating denervation requiring remyelinization of the nerve.

The frequency of sequelae is therefore highly dependent upon the time of incipient function. If this occurs within 2 weeks, only 5 get sequelae, but if it occurs after the second month nearly all the patients are left with sequelae.

Out of the idiopathic case 81 remitted completely, 10 % have negligible sequelae and 9 definite sequelae.

As far as the groups with herpes zoster and with polyneuritis are concerned, remission was slow, usually not starting until the 3rd or 4th month, and the majority — 12 out of 17 and 7 out of 8 respectively — got sequelae. However, it must be mentioned that this percentage is not higher than for those idiopathic cases whose remission was slow (19 out of 21).

Finally, it should be pointed out again that the object of the study is to show the spontaneous course of non traumatic peripheral facial palsy, not the effect of treatment. The patients only did mimic exercises a few times a day.

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ELECTRODIAGNOSIS IN FACIAL PALSY OF ENDOTEMPORAL ORIGIN

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46 patients suffering from different kinds of facial palsies f endotemporal origin have been closely examined. The nerve ability to transmit short electrical stimulus f one millisecond has also been examined. The investigation seems t shew that normal values for this examination predict a good prognosis. If the values between the healthy and paralysed sides are 3.5 milliampere or more on successive days, one cannot expect complete restitution after the paralysis, but must be prepared for sequelae of some sort. Th investigation also seems t confirm that paralysis which commences suddenly has a poorer prognosis than the paralysis which developes gradually If an improvement takes place within the first or second week after the appearance of paralysis, then the prognosis is good.

Facial paralysis is a serious condition in which mutilating changes take place in the patients appearance and in functions such as talking, eating and drinking The possibilities of spontaneous recovery in peripheral palsies vary from author to author probably depending upon the different criterias which are used

Taverner (1956) states that on subsequent investigation of patients with peripheral facial paralysis one will find that only 10 % are discontended with the final result of their disease. Cawthorne and Haynes (1956) on the contrary give a poorer prognosis. They found that in patients with Bell's palsy with a complete developed paralysis, full restitution occured in only 42 of the cases. After a six months period of observation 6% continued to be paralytic. On our department this observation has lead us to consider all cases of peripheral paralysis as possible candidates for surgical intervention with exposure of the facial nerve in its bony canal in the temporal bone. However the question has always been, when to operate.

Laumans and Jongkees (1963) divide the facial paralysis and their treatment into three groups.

Group 1 consists of herpes zoster oticus and syphilitic neuritis. In these cases the majority are agreed in conservative treatment.

Group 2 consists of paralysis due to chronic otitis, intratemporal tumours and facial paralysis which appears as an immediate conclusion to an ear operation, temporal bone fracture or trauma to the external ear or mastoid process. In these cases one must operate radically and as quickly as possible, exposing the facial nerve.

Group 3 are paralysis with Bell s palsy acute otitis and paralysis which occur after ear operations, temporal bone fractures or injuries to the external ear or mastoid process — but with a free interval of time between the injury and the appearance of paralysis. Here the usual treatment is primarily observative and conservative. If the paralysis persits, then a decompression operation should

be performed Just when to operate is difficult to say By operating one wishes to save the nerve from degenerating

The questions which arise when one is confronted with a patient with facial paralysis of endotemporal origin are·

1 Will the paralysis be transient, or with other words, is there a physiological and reversible block in the nerve?

2. If the paralysis is not reversible are there any signs or tests which can predict this prognosis?

Empirically one knows the following Cases in which the paralysis appears suddenly have a poor prognosis (Dalton 1960 Kettel 1965)

Cawthorne and Haynes (1956) found that partially paralysis usually recovers quickly Laumans and Jongkees (1963) state that the chances of complet restitution after a paralysis of one weeks duration are 50 %. The percentage falls rapidly towards zero after two weeks. In cases of partial paralysis the chances of full restitution after two weeks are 85 %. They have also found that when the muscle tone is good after two weeks, the prognosis is good. Kettel (1959) is of the opinion that occurrence of pain behind the ear is a bad prognostic sign. This is not verified by Laumans and Jongkees (1963) Blatt (1965) has examined the secretion of the submandibular gland and affirms by this aid to be able to decide the prognosis in Bell's palsy

So-called hyperacusis was found by Laumans and Jongkees (1963) to be four times more frequent in patients with incomplete restitution than in those in whom the restitution was complete The presence of naso-palpebral muscle reflex is by the same authors stated to be a good prognostic sign

Generally one can say that the clinical examination can not completely answer our questions. The question then is whether electrical tests can help us to classify our patients. The classification should be definite within two weeks, because after that time paralytic patients will have no chance of complete restitution (Laumans and Jongkees 1963).

We have two electrical test possibilities which will be described in more detail. Electromyography is the one. It is the registering of the individual motor units potentials. In cases with nerve degeneration one will find so-called fibrillations which are spontaneous action potentials of short duration low tension and rhythmic occurrence. Richardson (1963) states that they seldom occur before the tenth day after the appearance of the paralysis. Taverner (1956) means that fibrillations is a definite sign of degeneration, and says further that the diagnosis can be charted precisely by electromyography

Kettel (1959) is in agreement with this, but is of the opinion that electromyography is without value if one shall be able to pick out the patients for operation before the nerve has degenerated.

If fibrillations are envinced, then one can not count on complete restitution after the paralysis, but must be prepared for sequelae of some sort. The degeneration can strike some fibres while others remain normal. This can be the explanation of the rapid improvement one sometimes sees after facial nerve decompression

operations where the intervention saves those fibres which have as yet not begun to degenerate.

The most usual form for electrodiagnosis is by faradic and galvanic stimulation. In the way it is usually practiced it cannot be considered as a quantitive examination We have therefore in our department for some time used the nerve conduction test. We have applied the technique which is described by Cawthorne and Wilson (1963). The electrical stimulus is a square impuls with a different and indifferent electrode in which the voltage varies between 0 and 15 milliamperes and with a duration of one millisecond. The indifferent electrode is placed close to the stylomastoid foramen and the different electrode either centrally to the nerve junction or directly on the different branches of the nerve. The stimulus which only just causes a muscle contraction is noted daily

If a nerve injury blocks the nerve s conduction ability then stimulation centrally in relation to the injury will be unable to produce a contraction This loss of conduction ability can be due to any kind of nerve injury such as neuropraxia, axonotmesis or neurotmesis. If the nerve is stimulated distally to the lesion and no contraction occurs, then this must be due to degeneration of the peripheral part of the nerve — axonotmesis or neurotmesis. Cilliat and Taylor (1959) examined three patients in whom the nerve had been severed on account of *facial spasm. They discovered that the nerve lost its ability to transmit short* electrical stimulus of one millisecond, four days after the injury If the nerve injury causes a temporary block — neuropraxia — then stimulation of the nerve periferally to the block will produce a rapid and rigorous contraction.

In our department we have used the nerve conduction test since 1964 along with the usual diagnostic aids for peripheral facial paralysis.

TABLE 1

CIAL PALSIES ENDOTEMPORAL RIGIN. SURVEY O THE TIENT MATERIAL

Diagnosis	Number
Bells palsy	23
Fractures of the temporal bone with delayed onset	8
Operations on the temporal bone with a delayed onset	4
Paralysis in direct connection with operations on the temporal bone	3
Otitis media suppurativa acuta	1
Otitis media suppurativa chronica	2
Herpes zoster oticus	4
Meningitis serosa	1
Sum	46

Table 1 is a survey of the patient material. There have been 23 cases of Bell s palsy 8 patients with temporal bone fractures with a free interval of time between the injury and the appearance of paralysis and 4 cases of postoperative paralysis with a free interval of time between the operation and the onset of paralysis. We have further had 3 cases in which the paralysis occurred in direct conclusion to an operation. In one of these last cases the operation had been performed under local anaesthesia so that it is difficult to say exactly when the injury to the nerve

occurred. We have had one case of acute otitis with facial paralysis, two patients with chronic otitis and facial paralysis, four patients with herpes zoster oticus and one case of serous meningitis and facial paralysis.

TABLE 2
FINAL RESULT IN RELATION TO THE DURATION OF THE PARESIS

Duration	Sum	Normal function	Sequela	Paralysis
Until one week	7	6	1	
Until two weeks	19	1	2	
More than two weeks	20	4	10	6

Table 2 shows the final results as seen in relation to the time which elapsed before one saw the first movement in the face. In seven patients functioning began to return before a week had elapsed. Of these 6 patients have attained normal function while one case has a slight sequelae.

In 19 patients two weeks elapsed before any improvement was observed. Of these, 17 cases attained normal function and 2 have slight sequelae. The situation has been more serious where the paralysis has persisted more than two weeks.

In this group we have 20 patients and of these only 4 cases have attained normal function. In 10 patients we have registered sequelae of one kind or another and 6 of the patients are still paralytic. The registration period for four of these last six is rather short.

TABLE 3
FINAL RESULT IN RELATION TO INSTANTANEOUS OR GRADUAL COMMENCEMENT OF THE PARALYSIS

	Sum	Normal function	Sequelae	Paralysis
Suddenly beginning	16	5	7	4
Gradual beginning	30	22	6	2

Table 3 shows the final results in relation to the manner in which the paralysis arose. In 16 patients the paralysis started abruptly. Of these patients 5 have attained normal function, 7 cases have got sequelae and 4 are still paralytic. Of the last 4 patients the period of observation in two cases is too short to indicate the final result. In 30 patients there were a gradual development of paralysis. In this group 22 cases have attained normal function, 6 have some form of sequelae and two patients with too short observation period are still paralytic.

TABLE 4
FINAL RESULT AND THE NERVE CONDUCTION TEST (N.C.T.)

	Sum	Normal function	Sequela	Paralysis
NCT normal	26	26		
NCT patologic	20	1	13	6

Table 4 shows the registration of the nerve's electrical conduction ability 26 patients had normal conduction ability and all of these have attained normal function We have according to Laumans and Jongkees (1963) considered the values of the nerve conduction test as pathologic when the difference between the paralysed and the healthy side has been 3.5 milliampere or more on successive days.

We have found pathologic conduction ability in 20 patients. Of these twenty one has attained normal function. The pathologic values in this case came quite late in the course of the disease while the muscle function was in the process of becoming normal. 13 patients have some sort of sequelae and six continue paralysed.

We have not systematically examined the patients electromyographically Some of the patients we have operated before the elctromyography tests would have been of any interest However in 19 cases we have simultaneously done electromyography and nerve conduction registerings.

TABLE 5

THE NERVE CONDUCTION TEST (NCT) COMPARED WITH ELECTROMYOGRAPHY (EMG)

	Sum	EMG normal	EMG pathologic
NCT normal	5	2	3
NCT patologic	14	2	12

The results are shown in table 5 Of these 5 patients had normal values for the nerve conduction test, and of these five again, three had pathologic electromyograms, but all five patients attained normal function.

Pathologic values for the nerve conduction test were found in 14 patients, and of these two had normal electromyograms. But it must be added that registering of the electromyogram in these two cases were taken early in the course of the disease.

In 11 patients we have decompressed the facial nerve in its bony canal in the temporal bone. Two decompression operations were performed simultaneously with radical operations for chronic otitis. A third patient with chronic otitis shall be related in more detail.

A 20 year old man was admitted to the hospital because of chronic otitis. A radical operation was performed 12/2—66. When the patient woke up from the anaesthesia, a peripheral paralysis was observed on the operated side The nerve's electrical conduction ability continued normal for three days, but was extinct from the fourth post-operative day Electromyography 17 days after the operation showed no signs of activity either in the form of fibrillations or motor unit's potentials. 10 days after the first operation the facial nerve was exposed in its bony canal in the temporal bone and was found torn off at the level of the lateral semicircular canal. The ends were joined with a suture The patient is still paralytic, but the period of observation is too short to enable one to express any opinion about the final result. The patient is of great theoretic value since

this case demonstrates that the nerve retained its ability to transmit short electric stimulus of one millisecond for three days after the nerve had been severed. This finding is quite in keeping with what Gilliat and Taylor (1959) have demonstrated. As late as 17 days after the injury investigation with electromyography gave no information which might indicate the serious extent of the injury.

In conclusion we can state that we have found the nerve conduction test very useful. It has always proved to be right when it has indicated a good prognosis.

Except for one case which was described in more detail, we have always been able to predict a poor diagnosis. The material seems to confirm the theory that paralysis which commence suddenly have a poorer prognosis than those in which the paralysis develops gradually. If an improvement takes place within the first or second week after the appearance of paralysis then the prognosis is good. If the nerve retains its ability to transmit short electrical stimuli one can expect complete regression of the paralysis.

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ELECTROMYOGRAPHIC STUDIES OF FACIAL MUSCLE CO-ORDINATION DURING SPEECH

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The study of the neuromuscular basis for speech production is of great interest in speech research. The usefulness and importance of lip reading shows that the facial region transmits large amount of speech information. The muscles here are also easily accessibl for EMG work. However th stereotyped and easily reproduced speech gestures are also suitable for the study of the complex function of the facial muscles.

Th optimal electrode positions were found by first dissecting cadavers. The individual muscles of li ing person were located by palpation during voluntary contraction. After insertion of the needle its depth was adjusted to pick up the maximum activity during the performance of speech gestures.

The results from the first tudy covering all lip muscles are being used s the basis for further investigations which are partly presented here

The motor activity of the facial muscles during speech is regulated by central nervous impulse patterns and extremely well co-ordinated both temporally and spatially Therefore it may be more easily reproduced experimentally than any other voluntary muscle activity Electromyographic (EMG) studies of the easily accessible facial muscles are consequently of interest not only to the phonetician and phoniatrician, theoretically as well as practically but also to the muscle physiologist from a generally functional anatomical viewpoint.

The availability and importance of labiology shows what a surprising amount of linguistic information is supplied by the facial area.

We started with a general introductory study locating and registering motor unit activity from the electrode position representative of each muscle Later we systematically placed the electrodes circularly round the lips at intervals of 5 mm. Since the amount of overlap and interdigitation is much less at the origin of the muscle than at the insertion into the lips, we hoped to obtain separate recordings from each muscle by peripheral electrode positions. The fibres of a striated muscle usually run without interruption from one end of the muscle to the other and the EMG recording from either end should represent the activity in the rest of the muscle. At the analysis we defined muscle and its function from the action potentials and electrode position.

Concentric needle electrodes — type DISA — with a diameter of 0.3 mm are used. The motor unit potentials pass through an AC-amplifier to an oscilloscope for visual control and are recorded synchronously with the speech on a polychannel tape-recorder to be integrated and analysed later

The integrated EMG curves from repeated recordings of the same speech gesture are averaged and levelled in the following way The acoustic segment boundaries

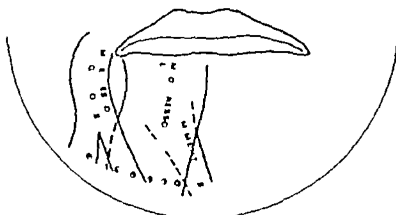


Fig 1

of the utterance are marked off The time displacements between different recording can be eliminated by averaging separately the electrical activity belonging to each sound segment These curves are then brought together to form the final mean EMG recording

Phonetic sounds which engage the lip muscles in closing rounding, opening, or spreading the lips are placed in a linguistic frame that prevents the speaker from overarticulation. From each electrode position the activity during five consecutive readings of the same sentence is recorded

Fig 1 shows the muscles of the chin, mentalis, depressor labii inferioris, and depressor anguli oris with a medial and a lateral portion The small circles mark the positions of the electrodes whose outputs are discussed in this paper

Fig 2 shows the averaged curves of the integrated motor unit activity from ten different electrode positions of the chin during the pronunciation of the bilabial consonants »p» and »b» under phonetically standardized conditions. The time segments embracing the reference or zero point — the moment when the lips close— display action potentials that are correlated with different phases of the speech gesture The peaks immediately to the left of the zero point in electrode positions 1 and 5—9 reflect the implosion or closing movement whereas the peaks just to the right in electrode positions 1—6 show the release activity of the consonant Electrode positions 2—4 represent exclusively m. depressor labii inferioris, 7 –9 solely m depressor anguli oris while 1 and 5—6 show overlapping medially between m. mentalis and m. depressor labii inferioris and laterally between m. depressor labii inferioris and m. depressor anguli oris. The closing movement — EMG peaks to the left of the zero point is thus produced by the depressor anguli oris and mentalis and the separation of the lips by the depressor labii inferioris with probable inhibition of the depressor anguli oris The implosion peaks are throughout slightly bigger for th voiceless plosive »p» than for the voiced »b» The release peaks, on the other hand are bigger for »b» than for »p». The difference can be explained by the fact that the vocal cords are abducted for »p» producing a higher intraoral pressure which must be counteracted by firmer lip-closure. In the opening phase the higher pressure facilitates the spreading of the lips, and less

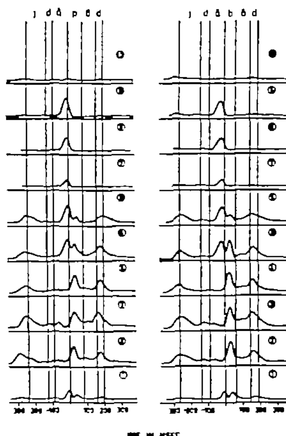


Fig. 2.

muscle energy is required than for the voiced cognate when the glottis is closed and the intraoral pressure lower

On the basis of dissecting studies on cadavers, palpation of the speaker's muscle contraction during speech, and EMG findings we suggest that in the production of a bilabial consonant the depressor anguli oris pulls the corners of the mouth downwards so that the upper lip becomes stretched and embraces the lower lip The mentalis pushes the lower lip upwards by pulling the skin of the chin-point upwards. *The release is brought about by the relaxation of these two muscles and* the contraction of the depressor labii inferioris, which pulls the lower lip downwards.

The vowel-combination »y» — »i» causes a rounding-spreading movement (see Fig 3). The zero point is here the moment when »y» proceeds to the non-labial consonant »d» The rounded phoneme »y» is preceded by a weak burst of activity in electrode positions 5—9 which is associated with the depressor anguli oris. Our continued investigations show that the lip-rounding is produced mainly by the orbicularis oris and that the activity recorded here must have an antagonistic function. Just before the succeeding spread vowel »i» a more prominent activity pattern appears in electrode positions 2—6, representing the depressor labii inferioris. When the rounded and spread vowels occur in the opposite order i» — y» the pattern at electrode positions 5—9 shifts over to the right of the zero point

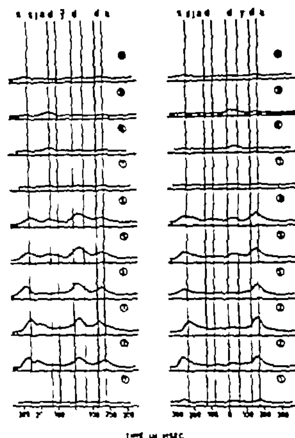


Fig 3

together with its vowel But now there is no spreading activity probably because the i is preceded by the spread vowels and in and this sound segment has a typical spreading pattern on the EMG recordings. Because of a presumable proprioceptive afferent activity or an adaptation effect a repeated central nervous muscle instruction fails to appear — it is functionally unnecessary in this co-articulation even though it is closely connected with the isolated speech gesture

The speech muscle activity is of great interest in speech research but only very few attempts to systematic EMG studies have been made And this few experiments were carried out with plate-electrodes, with which it is almost impossible to make interference-free detailed and differentiated studies. The results of our first experiments prove that electromyography can greatly help us to understand the neuro-muscular mechanism of the co-ordinated function of the facial muscles during speech

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A NEW APPROACH TO THE EXPERIMENTAL STUDY OF STUTTERING AND STRESS

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Almost one per cent f all people are st tterers. In spit of this high prevalence only ery few controlled psychopharmacological studies ha been published in this field. A modified double-blind technique for objective evaluation of biochemical and psychological drug effects is described. It combines a study of ( ) psychological and endocrin ffects of single doses of psychotropic and vegetotropic drugs, (b) the effects f long term treatment and ( ) pharmacological modification of experimentally induced psychological and endocrine stress reactions in 44 tutterers. An account is given f ( ) subjective feelings reported in questionnaires, (b) audio-and video-recorded speech behaviour and ( ) urinary catecholamine excretion as modified by different drugs.

Stuttering may be described as a disturbance in communicative behaviour composed of several factors: a dysfunction of the speech apparatus; the listener s reaction and behaviour when confronted with this dysfunction, the stutterer s immediate experience of the listener s reaction, real or imagined by the stutterer and projected on the listener and finally the secondary anticipation neurosis that most stutterers develop

Stuttering is an important medical problem. About one per cent of all people are stutterers. Until the middle of the last century stuttering was regarded as an organic neurological disease and was treated as such even surgically by cutting over muscles of the tongue. An extreme example in the opposite direction is provided by generalizing psychoanalytic theories of stuttering as an expression of sa restrained need to kill with words a form of exhibitionism or a regression to pregenital, oral satisfaction.

The predominant opinion at present is that stuttering is a co-ordination distur bance in an organically faultless speech apparatus. According to one of the most eminent investigators into stuttering of our time — Wendell Johnson of Iowa (Stuttering in Children and Adults, 1955) — the main reason for the origin of the disturbance could be the listener's, especially the parents more or less conscious reaction to the child s normal linguistic stumbling and hesitation during language development, known as iteration or physiologic stuttering The parents reaction makes the child conscious of his way of speaking Since the child experiences the parents reaction as critical and wants to come up to their expectations, he does his utmost to speak more fluently The child s efforts to avoid stuttering only too often result in so-called secondary stuttering The child enters a vicious circle, with increasingly strained attempts which only aggravate the stuttering

These repeated failures very often lead to mental disturbances. The stutterer may be able to disguise his speech defect from his surroundings, with or without the techniques imparted by logopedic treatment. Even so there will generally be a lack of self-confidence and a feeling of uncertainty vis-à-vis the listener in the speech situation. In clinical work one all too often meets with patients who are anxiety primed and depressed about their severe stutterings, even though objectively this can be neither heard nor seen. In many cases there is consequently a discrepancy between the stuttering as experienced by the stutterer and by those around him.

These conclusions are based mainly on clinical experience. Experimental studies are rare in this field. The relatively few psycho-pharmacologic tests have mostly not been truly double blind. This state of affairs was the background to the combined clinical-experimental study outlined here.

The main questions investigated were: (a) Is it possible to produce a subjective and/or an objective improvement in stuttering behaviour with the aid of a psychoactive drug? (b) Can placebo affect this behaviour, and if so, are there any differences between placebo and the active drug? (c) Which psychologic characteristics distinguish a group of stutterers from a matched group of normals or of patients of another kind? (d) How great are the feelings of discomfort reported by stutterers on being obliged to expose their speech disturbance in public? (e) How pronounced is the stress reaction elicited in their organism, as expressed by the urinary excretion of adrenal medullary stress hormones, adrenaline and noradrenaline (Euler 1964)? (f) Can these subjective and objective stress reactions be modified by short term (Leanderson & Levi 1967) and long-term treatment with a psychoactive drug?

Material and methods

The investigation was conducted with 44 adult patients, all of whom had suffered from stuttering since childhood. Their mean age was 29.5 years (range 19 to 48, 39 were men and 5 women, which approximately corresponds to the prevalent sex distribution within this patient population. All of them had received logopedic, many even medical therapy, in many cases during long periods, but in their own opinion with poor therapeutic results. Most of them belonged to the P-Club, a lay association of chronic stutterers. These patients were thus characterized by chronicity, resistance to therapy and a long history of the disturbance, while the extent of their manifest stuttering varied considerably.

Phase 1 of the investigation involved (a) a general medical and psychiatric anamnesis, and (b) a personality analysis and comparison of personality profiles on the basis of two questionnaires containing about 100 questions each. Furthermore the initial position before therapy as regards the patients' stuttering was defined on the basis of (c) a stuttering anamnesis, (d) the individual's subjective stuttering status (questionnaire), and (e) an objective stuttering status that included conventional tape recordings as well as televised speech behaviour under standardized conditions.

Phase 2 comprised (*f*) a double-blind medication lasting 2 × 27 days with a cross-over latin-square design. The drugs used were opipramol (Ensidon-Geigy) 50 mg × 3 and diazepam (Valium Roche) 5 mg × 3, in addition to placebo. The patients, however, were told that an unknown number of drugs would be used, that different patients would often but not always receive different drugs, and that some would be given pharmacologically inactive, blind tablets. They were also informed that the medication *might*, but would *not necessarily* vary from day to day. This ensured that the investigation was truly double-blind and that the patients really had to consider each day whether the current drug had any effect and if so, what.

At the end of each of the 54 days of treatment the subjects reported on a specially designed questionnaire (*g*) what had happened during the day, the mental and physical sensations they had experienced, and how much they had stuttered. The estimates were made on an 11-point scale ('extremely [anxious etc.] down to not at all') as well as with a magnitude estimation technique.

Moreover, at the end of each period of 27 days, a record was made of (*h*) the individual's objective and (*i*) subjective stuttering status, in the same manner as mentioned above.

On the 27th and 54th days, the subjects were exposed to an experimental situation supposed to be stress-inducing. A two-hour control period with standardized relaxed conditions was followed by a two-hour stress period during which the subjects, in a random sequence, repeatedly had to read texts and describe pictures projected onto a screen. In this way they were all kept in a state of expectation and speech preparedness. The time allotted for each of the tasks was brief and the limit strictly observed. Simultaneously recordings were made of psychical and bodily reactions as estimated by the subjects, their estimate of stuttering, objective stuttering (tape recording) and the urinary excretion of stress hormones (adrenaline and noradrenaline estimated according to Euler & Lishajko 1961). All details in the experimental setting were strictly standardized (Levi 1967).

Results

The investigation was concluded only recently and the numerous data are still being processed. Some results are evident from the raw data, however, and are presented tentatively here.

1. Subjective stress in the speech situation. Although it was observed during the speech situation that many of the patients were clearly embarassed and greatly inconvenienced, they reported only very moderate subjective effects in the questionnaire. This tallies with the clinical experience that patients of this type are definitely prone to avoid superlatives when describing their own speech experiences, possibly due to psychological defence (cf. Lazarus 1967).

2. Objective evidence of stress in the speech situation. It has previously been shown that changes in an individual's excretion of adrenaline may serve as an indicator of the level of stress in the organism (Euler & Lundberg 1954, Frankenhaeuser 1967, Levi 1963, Euler 1964). In experiments with subjects shown highly emotive films and exposed to trying working conditions the mean excretion of adrenaline

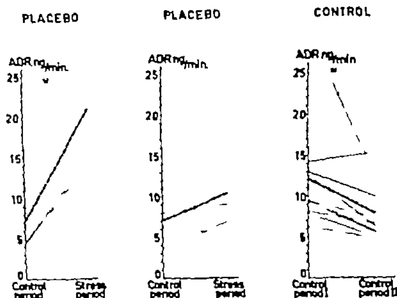


Fig. 1

was augmented but never by more than 100 per cent (Levi 1967). As shown in Fig. 1 (placebo-placebo-control) the speech situation was accompanied by a rise by almost 300 per cent. It may also be seen that a repetition of the situation — which is consequently made more familiar to the subjects — produced a definitely lower but nevertheless considerable increase from the control level before the speech situation. The true change was in fact greater, since the adrenaline excretion would normally have diminished considerably during the period in question, as demonstrated by the control experiments with stutterers not exposed to stressors (Leanderson & Levi 1967), the drop being due to diurnal variation (Levi 1960). It must

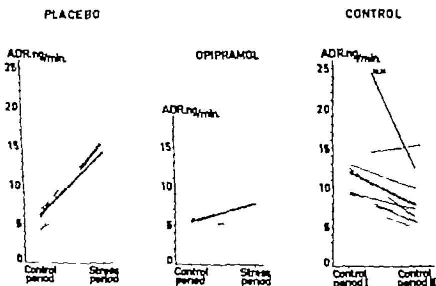


Fig. 2.

be concluded that the present subjects in spite of their statements to the contrary probably reacted with very considerable stress when obliged to perform verbally in public It seems improbable but can not be excluded that non-stutterers would react similarly This will be studied in a future investigation.

3 Influence of medication on endocrine reactions during acute stress It was expected on a priori grounds that psycho-active drugs with an undoubted influence on anxiety would be capable of depressing this high level of emotional arousal, as reflected in the adrenaline excretion. It may however be seen from Fig 2 (placebo-opipramol-control) that medication with opipramol for 27 days had little effect on the adrenaline exretion compared with the mere repetition of the situation.

4 Influence of medication on objective record of stuttering during acute stress. Neither of the psychopharmaca appeared to have a particularly marked effect upon the percentage of wrongly spoken words or the speech rate under stress. As a general trend, however long-term medication (51 days) with opipramol does reduce albeit moderately the percentage error and increase the speed of speech.

5 Influence of medication on the subject's estimated propensity to stutter during 27 days treatment As will be seen from Fig 3, the mean propensity to stutter is somewhat lower during treatment with opipramol compared with placebo medication, though the difference is not great. Moreover there is a tendency to a weekly cycle in the subject s estimates, with minima at the weekends. This suggests that, compared with leisure time and family life, the occupational environment is more provocative and conductive to stuttering

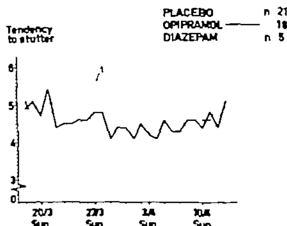


Fig. 3.

A more detailed report of the data is to be published

In conclusion it may be noted that the speech situation induces considerable objectively recordable stress reactions in stutterers and that these reactions can be modified to only a minor extent by the medication used in this experiment.

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DISCUSSION

H K Kristensen D Leanderson t ted that tuttering i a disturl ance of co-ordination in a int ct speech pparat W know of t gers in Copenhagen who perform skill lly before an audience but who t tter when they peak How is this t be xp lained? Can it be f importance therapeutically?

R Leanderso I d not l liev that st ttering can be cured with si ging e rcises, even though h thm t ming should be includ d in differentiated speech therapy

Z Islorff

Do you ha minations f patients with Parki son disease because these patients after a uccessful tereo-tactic operation in most cases till are oligomimic?

Leanderson I have myself pplied phoniatrics in the treatment of some patient with Parkin sonism both bef re and after tereotactic operation (Leksell). After a short period of practice the production of isolated phonemes was normal, whereas the co-articulation in the fluent speech did not fun tio even after a long course of treatment probably result of a degenerative central disorder f co-ordination

RADICAL REMOVAL OF CAROTID BODY TUMOUR

A CASE REPORT

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From th Otolary gological Hosp tal
(Head. Prof Urpo Siirala, Helsinki University)

A case report of 53-year-old woman having carotid body tumour is presented. The carotid body tumour is an uncommon pathological appearance The difficulty of making pre-operativ diagnosis f carotid body tumour is discussed. Arteriography is treated as the most useful diagnostic aid for an early discovery of this tumour Th fact that the operability of the tumour cannot be definitely determined until th surgical exploration, is emphasized. The tumour can become malignan t, but the degree f malignancy is low

A carotic body tumour in the neck is an uncommon pathological occurrence Only 400 cases have been presented in the literature

History

In 1743 von Haller first described the carotid body calling it »a ganglion minu tum» The microscopic structure of the carotic body was described by Luschka in 1862. He gave it the name »ganglion intercaroticum»

The first detailed description of the carotid body tumour and its operative removal was given by Marchand in 1891 The patient expired however on the third day after the operation. The first successful surgical removal of a carotid body tumour was performed by an American Scudder in 1903. The earliest description found in the Scandinavian literature is from the year 1916, when Wetterdal reports two cases of carotid body tumours, operated in 1914 and 1915 in Sweden. In Finland the carotid body tumour was first described in the literature in 1937 when Sonck described a carotid body tumour operated by Elving

The most comprehensive material on carotid body tumours is probably the work published by Phelps, Case and Snyder in 1937 They present a summary of 159 cases of histologically verified carotid body tumours.

The anatomy and physiology of the carotid body

The carotid body is situated in the neck, bilaterally at the bifurcation of the carotid artery or very close to it. Its size may vary average being about 6×4×2 mm. Its shape is ovoid. The colour is reddish brown and it is surrounded by a connective tissue capsule. Trabeculae radiating from the capsule divide it into small lobules. The carotid body is closely attached with the connective tissue capsule to the carotid artery mostly to the bifurcation and it receives its circulation from the carotid artery

The parenchyma of the carotid body is composed of rather large polygonal or cuboidal cells. The cytoplasm of the cells has great amounts of granules and vacuoles. The nucleus is round or oval containing small chromaffin particles. Characteristically the cells form groups or whirls and there are abundant capillaries in the stroma

The physiology of the carotid body is not yet fully understood but most authors believe that it functions as a chemoreceptor

Tumours of the carotid body

Pathology The tumour is practically the only pathological appearance of the carotid body The shape of the tumour is either round or ovoid its size varies from a diameter of 2 cm to one of 10 cm It lies near the bifurcation of the carotid artery and it is surrounded by the connective tissue capsule which attaches it firmly to the carotid artery

It is most often histologically benign, but it can become malignant according to most authors in 10 to 20 per cent of the cases, and according to Harrington et al. (1941) in up to 50 per cent It is usually difficult to prognosticate the malignancy on the basis of the histological picture but diagnosis can be based on tumour growth and invasion of adjacent tissues.

Microscopic structure Many carotid body tumours are histologically similar to normal carotid bodies. They are composed of epitheloid islands which are surrounded by vascular stroma Mitoses or other evidences of malignancy are not usually found The numerous capillaries in the fibrotic stroma are typical histological findings in carotid body tumours (Saphir 1950)

Le Compte (1948) divides the tumours into three histological types. The first type has a structure resembling that of a normal carotid body This is the most common type

The second type resembles an adenoma. The cells are clearly of epithelial origin being round or polygonal with abundant cytoplasm They generally form lines or rows and stroma is scarce

The third angiomic type has ovoid or crescent shaped cells which resemble endothel cells.

Clinical findings

The tumour lies deep in the neck near the angle of the mandible Palpation reveals rubberlike consistency and pulsation of the carotid artery can be felt It moves laterally but not vertically and does not move when swallowing

Carotid body tumours occur equally in both sexes. It can appear at any age although most often in adults In the material collected by Phelps et al. 90 per cent of the tumours appeared at an age between 20 and 60 The tumour is generally unilateral, but according to Engström and Hamberger (1957) bilateral tumours are not uncommon. Family disposition has also been described in the literature, although it seems to be very unusual (Lewison et al., 1950)

Symptoms

The growth of the tumour is very slow and its symptoms are few For this reason the patient does not seek medical help until several years after noticing a swelling on the neck. The average history of the tumour was 7 years in 118 cases in the material collected by Phelps et al. As the tumour often pulsates owing to the proximity of the carotid artery it can be mistaken for carotid aneurysm The tumour becomes clinically malignant when by pressure it causes symptoms in the surrounding nerves and blood vessels. As the compression of the carotid artery increases, the patient may have attacks of dizziness, a feeling of weakness and headache Involvement of the vagus, sympaticus as well as the hypoglossal and glossopharyngeal nerves may cause symptoms of hoarseness, Horner s syndrome dyspnea, cough and swallowing difficulties.

Carotid body tumours are generally benign or only locally invasive. A total of 25 histologically proved cases have, however been described, where metastases have been found in the regional lymphatic glands or in more distant organs. The symptoms caused by distant metastases vary depending on the involved organ (Romanski, 1954, Fanning elt a., 1963)

Case report

The patient is a 53 year old woman who was hospitalized on April 5th, 1965 In 1959 she was found to ha e a medium-sized tumour in the neck, and biopsy was done at the local hospital. The histological picture of the biopsy was suspicious of tuberculosis. The patient was given a combined tuberculosis treatment (SM+ PAS+INH). About three months after the beginning of the treatment streptomycin was discontinued because the patient developed sensitivity to the drug She remained under treatment of the tuberculosis specialist and continued to take INH and PAS for five years. However as the tumour continued to grow slowly and was comparatively firm in its consistency she was sent for surgical consultation. She was subsequently referred to the otolaryngological hospital of the University of Helsinki.

In the investigation of the patient a 5×10 cm large firm tumour was found on the right side of the neck. It was relatively fixed and did not move when swallowing On palpation it was not tender and no pulsations were noticed The x-ray of the thorax was negative as was the sputum specimen. The sedimentation rate was slightly elevated Neither arteriography nor jugulography were performed Tentative diagnosis before surgery was tuberculotic lymphadenitis with a metastatic or primary malignancy of the lymphatics to be ruled out. Exploratory surgery on April 7th, 1965 revealed a smooth reddish brown tumour which was adherent to the bifurcation of the carotid artery It was now evident that the lesion was a carotid body tumour Pressure of the tumour had caused almost complete occlusion of the internal carotid artery The external carotid artery was also noticeably occluded. The tumour had infiltrated the wall of the artery at the bifurcation and also invaded the vagus and hypoglossal nerves (Fig 1). The tumour was removed radically after the common carotid artery was ligated, and the nerves mentioned above had to be sacrificed with the excision



Fig. 1

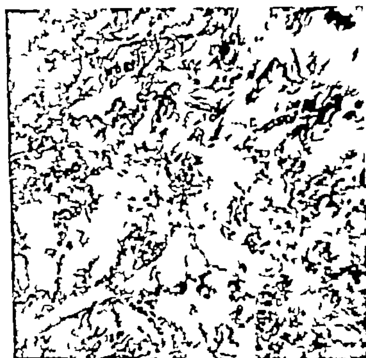


Fig. 2.

specimen was submitted to the pathologist and his diagnosis was carotid umour Le Compte s type 1 (Fig 2)
n the patient recovered from anaesthesia her voice was found to be hoarse, ere were no symptoms of paresis or hemiplegia. On the day following the

operation the patient had difficulty swallowing and a nasogastric feeding tube was inserted. Neurological consultation revealed paralysis of the vagus, hypoglossal and glossopharyngeal nerves on the right side. As no improvement of the swallowing was noted during the next three days gastrostomy was performed. Twelve days after this operation the patient was able to swallow well again. The gastrostomy was closed and she was released from the hospital. Re-examination half a year after the operation showed only slight hoarseness. There was no dyspnoea. In the phoniatric investigation the right vocal cord was found to be in a paramedial position, but slight movement of the cord was present. In phonation the rima glottidis remained 1 mm open. She had no swallowing difficulties, and the scar on the neck was well healed with no evidence of recurrence of her disease.

Discussion

A *carotid body tumour is to be suspected when a slowly growing mass is discovered* deep in the neck, close to the mandible angle, particularly when symptoms are few

A metastatic malignancy differs from the carotid body tumour by its irregular shape, firmer consistency and more limited mobility Metastatic nodes are usually more numerous and grow rapidly

The position of the branchial cyst is usually below the carotid bifurcation and the tumour is more superficial than the carotid body tumour

The differential diagnosis between thyroid tumours and carotid body tumours might sometimes be difficult. The thyroid tumour does not usually lie deep between the internal jugular vein and the sternocleidomastoideus muscle. The thyroid tumour does not pulsate and it moves vertically when swallowing

Lymphomas and abscesses should be kept in mind in differential diagnosis. But these usually grow more rapidly than carotid body tumours.

Neurofibroma also appears in the neck, and it is probably impossible to differentiate it from the carotid body tumour other than by exploration.

When a pulsating tumour is found in the neck the possibility of a carotid aneurysm should be considered. Angiography confirms the diagnosis and needle biopsy is of course contraindicated.

Pre-operative diagnosis of carotid body tumour is extremely difficult to make. In Lahey s and Warren s (1947) material the correct pre-operative diagnosis was made in 9 cases out of 18, and in Phelps et al. the pre-operative diagnosis was correct in 12 cases out of 159 Thus a surgeon may make the diagnosis of carotid body tumour only by exploratory surgery and thereafter must decide whether radical excision should be performed.

How can we improve the possibility of making the correct pre-operative diagnosis in the case of a deep-lying neck tumour?

The only certain method for this would be needle biopsy In needle biopsy the danger of bleeding is great, however particularly when a tumour lies deep in the neck. Most authors in the literature do not advocate needle biopsy For the same reason incision biopsy is risky

Jugulography is a very valuable aid in the diagnosis of glomus jugulare tumours in the ear area but with carotid body tumours in the neck it does not offer helpful information, especially when the tumour is small

Carotid angiography is the most valuable diagnostic aid when a carotid body tumour is suspected Conley (1963) considers it a very useful method in the verification of small carotid body tumours. In his opinion it gives valuable information about the size and location of the tumour its relation to the carotid artery and the possibility of obstruction to the vital arteries and subsequent collateral circulation It would be ideal to perform carotid angiography as a routine in all cases of tumours lying deep in the neck All too frequently the diagnosis of carotid body tumour is not made until the neck is explored and this may be avoided by having a high index of suspicion and performing angiography more frequently

Treatment

The ideal treatment is total excision However there is a great danger connected with this operation, especially when ligations of the common carotid or internal carotid arteries are necessary In Conley s material of 21 patients, 20 were operated on, and the mortality was 12 per cent Another 12 percent of the surviving patients suffered from post-operative hemiplegia Phelps et al. reported that 148 of the 150 patients had excisional surgery In this group the operative mortality was 24 per cent and when the carotid artery was ligated the mortality was 30 per cent. Of the remaining surviving patients 21 per cent had various complications, involving the nerves or the circulation

It might also be mentioned that in the paper of Phelps et al. 7 patients were treated with x-ray without benefit They also reported a 7 per cent recurrence rate within one year after excision

When planning surgical attack on a carotid body tumour the following should be considered

1) In 75 per cent of the cases the tumour is almost without symptoms and in the remaining 25 per cent the symptoms are usually slight
2) The growth of the tumour is usually very slow
3) Malignancy has been found in 15—20 per cent but mostly of a very low degree.
4) Operation is usually not recommendable for patients over 50 if the vital carotid arteries must be ligated
5) Operation should always be attempted when the tumour has invaded the throat to such an extent that the patient has swallowing and breathing difficulties.

Conclusion

In the case presented the tumour had infiltrated the wall of the bifurcation of the carotid artery and there was an obvious danger of spontaneous perforation of the vessel. Moreover the tumour had by pressure caused almost complete occlusion of the internal carotid artery and the lumen of the external carotid artery

was also decreased markedly The tumour had infiltrated the vagus, hypoglossal and glossopharyngeal nerves so that they could not be preserved and their sacrifice was mandatory Circulation disturbancies were not expected as the collateral circulation was sufficiently developed owing to the prolonged compression of the vital arteries.

The patient compensated very well in a relatively short time to the sacrifice of the cranial nerves. Her voice returned to nearly normal in six months with good production of speech and adequate facilities of communication.

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DISCUSSION

Peter Berdal Oslo Norway:

Some of the carotid body tumours produce catecholamines partly in considerable quantities. In one of our cases the urinary elimination of noradrenaline was 430 μg in 24 hours (the normal values being 10–60 μg). The content of noradrenaline in the tumour was in one specimen 550 μg/g tumour tissue and in another specimen it was 2100 μg/g. The adrenalin values were only 33 and 10 μg in the same specimens. Twenty four hours after the extirpation of the tumour the urine showed normal catecholamin values.

To be able to proceed saf ly during surgical removal of the tumour it is necessary to examine a possible production of catecholamines by urine analyses. It is also necessary to register the blood pressure continously during the operation. Death has occurred immediately after the removal of the tumours due to fall of the blood pressure.

In some cases of carotid body tumours the growth is so intimately connected with the internal carotid artery and even th common carotid that separation of the tumours from the vessels is impossible. A surgical removal which necessitates resection of the internal carotid artery may give rise to serious disturbance of the cerebral circulation. The influence on cerebral circulation of obstructing the common carotid artery can to some extent be examined preoperatively by electroencephalographic and angiographic methods. The influence on the cerebrum should also be examined during the operation by electroencephalography combined with intermittent compressions of the involved arteries. If obstruction of the carotid passage brings about marked electroencephalographic changes it is preferable to refrain from surgical removal except for biopsy and if desired replace surgery by X-ray treatment of the tumour

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FLUORESCENT MICROSCOPY IN NASAL CYTOLOGY

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Fluorescent microscopy has achieved permanent significance in basic as well as in clinic research. The acridine orange method is generally used in exfoliative cytology Its significance in gynaecologic cytology is very much discussed and the opinions of different authors ary The present investigation in nasal cytology has shown that it has no dvantages over other methods used in routine investigation, such as for instance Papanicolaou s staining method. On the other hand it is of importance in basic research when additional information about the physiological and pathological changes in the mucous membrane is sought. In my opinion — which deviates from statements found in the literature on the subject — the acridine orange method also gives clear picture of morphological cell structures. The histochemical findings through the use f the acridine orange method did not really contribute anything specifically new but they were very interesting on their part. Thus the DNA and RNA contents were clearly visible in different cells. Mucopolysaccharides also showed distinctive colour in goblet cells.

The application of fluorescent microscopical methods to cytopathology has become more and more important during recent years.

To more fully understand the phenomenon of fluorescence I will start with a short theoretical introduction.

Light is an electromagnetical wave of periodic oscillation. When such a wave hits the molecule it causes a certain oscillation in electrons and a new field of energy results. In other words, the molecule has absorbed light. In the visible spectrum the range of wavelengths ranges from 800 mμ to 400 mμ and the different wavelengths give us the sensation of red, orange, yellow green, blue and violet light. The ultraviolet region of the spectrum has wavelengths which we cannot see. The process of fluorescence consists in the conversion of short invisible wavelengths into longer visible waves. In other words, the ultraviolet light may become visible in microscopy by excitation of tissue specimens which contain fluorescent material.

There are two types of fluorescence. First. When a substance is placed in the dark and excited by ultraviolet light it becomes visible. This phenomenon is called primary fluorescence, autofluorescence or natural fluorescence For example glandular tissues, such as apocrine glands, adrenal cortex, thyroid, testis and liver have natural fluorescence when excited by ultraviolet radiation. Skin, fingernail, ganglion cells and lipoid tissue are also markedly fluorescent. Compounds such as porfyrins, hemosiderin, melanin, argentaffin granules and vitamin A are well-known fluorescent substances. All of these are able to absorb the invisible ultraviolet radia-

When the paper was presented fifteen coloured pictures were hown.

tion and transform it by fluorescence into different colours which are within the visible range and can be observed directly through a microscope

Second. Secondary fluorescence or fluorochromasia results from the treatment of tissue specimens with fluorescent materials or fluorochromes. There are several fluorescent dyes such as acridine orange thioflavin S, thioflavin T rhodamin B and primulin, each used for specific purposes.

A very important application of fluorescent methods is »the anti-body-technique» developed by Coons and his co-workers. In this method anti-bodies can be conjugated with fluorescent dyes in order to locate antigens in the tissues of the body

Acridine orange

Many fluorescent dyes have been tested but as Wied and others (1962) have showed in their investigations, acridine orange has been found to be the most successful both in cytology and in microbiology L. von Bertalanffy F Masin and L. Masin (1956) developed what is now the most widely used technique for staining of cytological smears with acridine orange. In his article F D Bertalanffy (1962) highly recommends the microcrome acridine orange produced by E. Gurr and the acridine orange produced by G T Gurr as the best stains for the fluorescent method.

Histochemistry of acridine orange and its cytochemical basis

The Soviet scientist Meissel (1951) was the first to discover that desoxyribonucleic acid (DNA) and ribonucleic acid (RNA) give different colours with acridine orange if the pH is properly adjusted

The chemical components of the cells which probably have the greatest significance in cytodiagnosis are the nucleic acids. Nucleoproteins are conjugated proteins in which the prosthetic group is nucleic acid DNA is situated only in the nucleus. The arrangement of different nucleotides and DNA-molecules provides the various kinds of information which will determine the composition of the cells. The modern concept of the gene is that it is a segment of DNA molecule containing a particular nucleotide sequence. The Feulgen reaction is a histochemical test for DNA which follows the principle that hydrochloric acid liberates aldehydes from the sugar of DNA, but not from the sugar of RNA The other nucleic acid, RNA is situated in the nucleolus and in the cytoplasm All or at least most of the cytoplasmic RNA is synthesized in the nucleolus. From the nucleolus it probably passes to the cytoplasm through the nuclear pores. The cytoplasmic RNA controls protein synthesis. Cells which synthesize protein contain moderate amounts of cytoplasmic RNA whereas others not engaged in this activity have little or no RNA. One reason for protein synthesis is the elaboration of proteincontaining secretion material. Protein synthesis is also necessary for growth regeneration and cell renewal For example, basal cells in epithelium dividing at moderate rates contain more RNA than more highly differentiated superficial cells. Rapidly proliferating malignant cells may contain large amounts of RNA Likewise are large amounts of DNA generally produced in the nuclei of malignant cells during a rapid abnormal mitotic process.

The fluorescent method utilizes the principles underlying these cytochemical phenomena. Acridine orange can be a specific stain for nucleic acid under certain conditions. However at low pH other substances with free acidic groups such as acid mucopolysaccharides will also bind with acridine orange. Nuclear DNA fluoresces green; dense, pyknotic and hyperchromatic nuclei are yellowish green or yellow Cytoplasmic and nuclear RNA appears in the spectrum ranging from brown to bright red. Cells with little RNA show brown cells with moderate amounts of reddish brown and cells with large amounts of RNA show bright orange to flaming red cytoplasmic fluorescence When the cells do not contain RNA the cytoplasm is greenish or remains unstained

Acridine orange fluorescent techniques

The most commonly used technique of acridine orange is the original method developed by L von Bertalanffy and others in 1956 This is a combined cytochemical-morphologic method It is applied primarily to smear preparations fixed in alcohol-ether alcohol alone or in ethylalcohol substitutes.

The other method which is often used is a modification by Dart and Turner (1959) The main difference between the original method and the modification is that the latter uses an organic citric acid buffer (McIlvaines buffer) at pH 3,8 instead of the inorganic buffer of the original technique. I will deal with both these methods in detail later on in connection with my own investigations.

There are several other modifications of the acridine orange technique, as for example. 1) The rapid one-minute modification by F D Bertalanffy and Nagy where the histochemical reactions are identical with the original method. According to the authors the fluorescent picture is similar The smears are processed by the original 6-minute procedure or by this one-minute modification. 2) The acridine orange-sodium chloride technique developed by Riva and Turner (1962) is not actually a cytochemical procedure. It is useful purely as a morphological procedure without any of the disadvantages of the original fluorescent technique. 3) Vital and supravital acridine orange staining techniques are used for cytodiagnosis of body effusions, urine, blood and bone marrow (F D Bertalanffy 1962).

Previous work on acridine orange

F D Bertalanffy (1962) gives a comprehensive review of previous literature on the use of acridine orange in cytology He states that the acridine orange fluorescent method has been successfully applied in cytodiagnosis of many thousand cases. Most of these studies have been made in the field of gynaecology The main purpose of the method has been the prescreening of specimens to detect the presence of malignant cells as indicated by the red colour of the cytoplasm. The final diagnosis has been done however on morphological grounds by cytologists or cytopathologists.

Not so much work has been done on the respiratory tract and to the best of my knowledge, none on the nose using the acridine orange method. According to

F. D. Bertalanffy's review there are 8.860 other exfoliated material among the 50.000 cases of exfoliated material. This group includes all other kinds of cytological material besides respiratory secretions, urine, pleural fluid, ascitic fluid, gastric washing etc. The major importance of the screening has always been the detection of malignancy. Very few observations have been made of the cytology of non-malignant diseases (Brown and Vello 1961, F. D. Bertalanffy 1962; Wied et al., 1962). There is no systematic work which would give the cytological patterns of non-malignant diseases of the nose and other respiratory tracts when using the acridine orange fluorescent technique.

There are different opinions about the accuracy of the acridine orange fluorescent technique. According to the review of F. D. Bertalanffy there are many successful studies in this field. Several workers have tested the diagnostic reliability of the fluorescent method by use of some conventional cytodiagnostic method, usually Papanicolaou's method. These comparisons are made either on identical smears or on different smears from the same exfoliated specimens. According to F. D. Bertalanffy the reliability of the acridine orange fluorescent method is remarkable considering that the method still lacks standardization and that it has been in use only for a short time.

Quite opposite opinions can also be found. Liu (1961) criticizes the method strongly in his article. In his summary he claims that the fluorescent method with acridine orange is not a better screening method than that of Papanicolaou and that it gives much poorer morphological details. Wellman (1963) agrees with Liu. He states that the method is not to be recommended as a routine method and that it is neither safe nor economical.

In the conclusion of his review F.D. Bertalanffy emphasizes the fact that one must strictly follow the steps of the original acridine orange fluorescent technique in order to obtain optimal results. Another important thing is, according to him, the correct pH, because the specificity of acridine orange is achieved only within a limited pH range.

OWN OBSERVATIONS

Material and methods

The present study is based on nasal specimens obtained from otorhinolaryngological patients. The specimens were examined by the acridine orange fluorescent method. Two AO[1]) methods were used, that is the original AO method developed by Ludwig von Bertalanffy and others, and the modification developed by Dart and Turner.

Fixation

The specimens were fixed either in alcohol-ether 1:1 or using carbowaxin. There was no difference to be seen in the cytological picture after these two fixing methods. The minimum fixation time was fifteen minutes when alcohol-ether was used.

[1]) Acridine orange abb. AO

Staining solutions

In the original method the AO staining solution was prepared in the laboratory First it was prepared as a 0.1 % stock solution. Then using pH 6 buffer solution it was diluted to a 0 01 % working solution. The phosphate buffer pH 6 was made by using 6 parts of 1/15 M KH_2PO_4 (in aqua dest.) and 1 part of 1/15 M Na_2HPO_4 (in aqua dest.). The calcium chloride solution which was used for differentiation of nuclei was an aqueus 0 10 M $CaCl_2$ solution

In the modified method of Dart and Turner the same AO staining solution was used. The buffer solution in this method was different. McIlvaine s organic citric acid-Na_2HPO_4 buffer at pH 3.8 was used instead of the inorganic buffer of the ori ginal technique. As this buffer also extracts nucleic acid-bound AO differentiation in $CaCl_2$ is unnecessary

Staining procedures

The directions given by L. von Bertalanffy in his original acridine orange method were strictly followed. The pH of the buffer solution was checked at the date of the fixation and if the buffer was stored in a refrigerator its pH remained extremely constant. The working solution of AO was repaired weekly and was also stored in a refrigerator The different steps of the technique used were:

1) If the specimen was fixed in alcohol-ether it had to be used immediately in the staining procedure. The carbowaxin-fixed specimens were rinsed briefly in 95 % alcohol before the original procedure.

2) Smears were rapidly rinsed in 80 %, 70 %, 50 % alcohol, and in distilled water for hydration.

3) They were passed through 1 % acetic acid to prevent rapid fading of fluorescence (according to F D Bertalanffy) and again through distilled water

4) Smears were stained in the 0 01 % AO staining solution for 3 minutes.

5) Smears were placed for 1 minute in phosphate buffer at pH 6 to remove ex cessive dye.

6) For differentiation the smears were placed in 0 10 M calcium chloride for 1—2 minutes until the nuclei appeared in clear translucent fluorescence.

7) Smears were rinsed with phosphate buffer which removes calcium chloride and thus halts differentiation.

8) The wet smears were covered with cover glasses.

The entire procedure took only 6—7 minutes.

The other staining method used was the modification of Dart and Turner (1959). Fixation was the same as in the original method.

1) For hydration the smears were dipped 5 times in 80 %, 70 % and 50 % alcohol

2) Then they were dipped 4 times in 1 % acetic acid.

3) Slides were rinsed in distilled water for two minutes.

4) They were transferred to McIlvaine s buffer at pH 3.8 for 3 minutes.

5) They were stained in buffered acridine orange 0 01 % for 3 minutes.

6) Smears were differentiated in McIlvaine s buffer for 4 minutes.

7) The excess material at the ends of the slides was wiped off gently with blotting paper

8) The cover glass was applied with buffer and the slides were allowed to stand 2 minutes before examination.

In both methods the slides can be restained or stained with Papanicolaou after having been destained by immersion in 50 % alcohol for a few minutes.

If the slides became dry during the examination it was useful to add buffer solution in order to prevent the bright colour of acridine orange from interfering with the fluorescence.

For storage F D Bertalanffy recommends, first removal of the cover glass, then careful immersion of the smears in distilled water They may then be returned to the buffer for re-examination within a few hours, destained in 50 % alcohol, or returned to fixative. Alternatively they may be dried and filed

Equipment in fluorescent microscopy

The light source for fluorescent microscopy is usually a high pressure mercury arc lamp which gives sufficient energy in the ultraviolet and blue regions of the spectrum (wavelength 150 mμ to 380 mμ)

To remove the unwanted visible light efficient filters for the visible spectrum must be used These filters are called exiter or transmission filters. To remove the red region of the spectrum which causes heat in the specimen, extra heat filters have to be used. The barrier or suppression filters are used to remove the ultraviolet light from the oculars and so protect the eyes of the microscopist and secondly these filters create the dark background

The microscope used in the present study was an ordinary lightmicroscope with a good mirror

The microscope slides had a thickness of 1 00 mm to 1 1 mm and the coverglasses were also of a special kind The immersion oil was of a non-fluorescing type

Findings

Patterns in the normal nose

In almost all the specimens characteristic squamous cells could be found. The cytoplasm of anucleate and superficial squamous cells showed transparent green fluorescence. Most of the squamous cells were superficial with pyknotic nuclei which showed a brilliant yellowish-green fluorescence. Cornified cells could not be differentiated from non-cornified cells. Less mature squamous cells had larger nuclei with similar fluorescence. In the cytoplasm of these cells orange granules could be found when the usual fluorescence was green The origin of these squamous cells was obviously the vestibulum nasi and the border of the mucous membrane and the squamous epithelium.

The normal ciliated columnar cells showed clear distinctive fluorescence. The nuclear fluorescence was yellowish green and chromatin structure was often beautifully visible. The cilia were also visible but they did not give any special

fluorescence. In the cytoplasm of the normal ciliated cells bright red granules could now and then be seen. The reddish fluorescence was also present in some nucleoli of the normal ciliated cells. Parabasal and basal cells often had reddish fluorescence in the cytoplasm, and nucleoli had almost always the same fluorescence whereas the nuclei had orange-yellow fluorescence.

In the normal nasal secretion a few leucocytes could almost always be seen Polymorphonuclear cells had bright yellow nuclear fluorescence. On the other hand the cytoplasm of these cells was gray almost colourless.

Lymphocytes had a reddish cytoplasm and yellow-green nuclei, and sometimes they were not easily distinguishable from basal and parabasal cells. The nuclei of lymphocytes were, however more dense than those of basal cells.

The complete lack of fluorescence of erythrocytes was a distinct advantage in the examination of bloody specimens.

Patterns of acute infections (Common cold)

There is a comprehensive study of cellular patterns of common cold by Bryan et Bryan (1950, 1953, 1959). They found very interesting changes in the nuclear structure of the cells studied during common cold. The same changes were clearly visible when the acridine orange fluorescent method was used in the present work. All of the different morphological variations could be seen distinctly

The marginal arrangement of the basophilic chromatin in the nuclei was not so clear as in Papanicolaou's stain, but much more distinctive than in Wright's staining method. The karyorrhexis with irregularly distributed pyknotic clumps of chromatin and inclusion bodies were very distinctive The halo was also clearly visible. The change appearing most often in common cold is a pyknotic form of a degenerated nucleus. These changes were beautifully visualized in the present technique. These nuclear variations showed dense yellowish fluorescence. In a very active virus infection broken epithelial cells or tufts were also distinctly visible The fluorescence of the cytoplasm varied. Usually the colour was gray-yellowish, but particularly in the beginning of the infection one could see red spots in the cytoplasm, and sometimes its colour was homogeneously reddish. Usually it was easy to distinguish these degenerated cells from other elements of specimens. In common cold one could see different numbers of polymorphonucleated leucocytes, which were easily distinguishable because of their smaller size and the clarity of their lobed nuclei.

Patterns in chronic infection

The polymorphonucleated leucocytes with a bright yellow nuclear fluorescence were prominent elements in the chronic nasal infection. Bacteria were also numerous, and they had a very distinctive reddish colour Morphological features were astonishingly clear and it might be possible after further studies to differentiate between different kinds of bacteria by using the acridine orange fluorescence method.

Patterns of ozaena

In the smears of this disease polymorphonucleated leucocytes and bacteria were also extremely numerous. Here one could see more degenerated white blood cells and mucoid elements than in the usual chronic nasal infection. They were easily distinguishable from epithelial cells and other elements by their typical fluorescence. The marked edema of nuclei of columnar epithelial cells were also distinctive in the acridine orange technique. One could see bright yellow chromatin clumps in these cells. The nuclear borders were distinctive, although the cytoplasm was unclear Often one could see large naked nuclei with edematous alterations. When the cytoplasm was visible it was gray in colour without marked fluorescence. Metaplastic cells showed a colourful fluorescence. Their nuclei were bright yellow and the cytoplasm was usually gray-green with little brownish granules. Occasionally one could see vacuoles in the cytoplasm of metaplastic cells. Bacteria in the smears from ozaena were bright red and very often they were edematous

Patterns of allergic rhinitis

The eosinophilic and basophilic granules of the mononuclear cells did not show any special fluorescence. The nuclei of these cells had an orange -yellowish colour similar to that of polymorphonucleated leucocytes, but the cytoplasm had gray green almost colourless fluorescence. On the other hand the goblet cells showed brown to reddish cytoplasmic fluorescence and their nuclei were yellow-green.

DISCUSSION

Fluorescent microscopy has achieved permanent significance in basic as well as in clinic research. The acridine orange method is in general use in exfoliative cytology as a screening method but it has by no means been able to replace Papanicolaou s staining method. Many authors have pointed out that the acridine orange method is not intended to be a morphological method, but that its significance as a diagnostic tool lies almost entirely in the histochemical changes which can be observed in the cells by the help of acridine orange.

The acridine orange fluorescence screening method has its own position in gynaecologic and bronchologic cancer cytology Has the acridine orange method then any practical significance in nasal cytology? In my opinion — deviating from statements found in the literature on the subject — the acridine orange method gives a clear picture of morphological cells. It does not, however quite reach the morphological level attained when using Papanicolaou s staining On the other hand, it gives a morphologically better picture of the cells than for instance eosin staining or Wright s staining method do

The histochemical findings through the use of the acridine orange fluorescence method did not really contribute anything specifically new but on their part they were very interesting Acridine orange is a basal dye the molecules of which irrespective of concentration have a yellowish-green fluorescence. The amount of dye absorbed by the tissue particles increases with prolonged staining time, in the same

way as the amount of absorbed dye increases with the concentration of the dye. It is also strictly dependent on the pH value of the solution. Being a basal dye acridine orange binds especially with tissue particles so that it expressly seeks to concentrate in cells which contain large amounts of acid mucopolysaccharides or nucleic acids. What is then the reason that tissue particles which contain large amounts of DNA have a green or yellow fluorescence, whereas tissue particles containing a lot of RNA have an orange or red fluorescence? This is quite obviously due to the degree of polymerization of the acids. This is higher in DNA than in RNA. If the DN acids are depolymerized by treatment with acids, its yellow fluorescence changes into red according to Schümmelfeder et al. (1952). The fluorescence caused by acid mucopolysaccharides is due to the pH value and possibly also to the degree of polymerization.

It should be noted that efforts were made to keep the staining conditions as similar as possible by frequent checking of the pH value of the solutions and by keeping the staining time and the concentration of the dye strictly analogous.

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ENDOCRINE STIMULATION OF HEALING

A STUDY OF COLLAGEN FORMATION AND WOUND TENSILE STRENGTH IN PREGNANT RATS

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Clinical observations on pregnant women, e.g. of gingival fibro-haemangioma, of increased keloid formation in scars and of healing of peptic ulcer support the hypothesis that tissue formation and healing might be stimulated during pregnancy. Collagen formation in subcutaneous sponge implants was studied in pregnant rats. In 5 days old sponge implants from the first week of pregnancy the hydroxyproline concentration and the total amount of hydroxyproline were significantly increased. The results indicated that collagen formation as well as the formation of granulation tissue were stimulated during this phase of pregnancy in the rat.

Determinations of the tensile strength of healing skin incisions showed that the collagen formed in the healing tissue was of functional importance. The tensile strength of 5 days old skin incisions was significantly increased during the first week of pregnancy in the rat. During the third week of pregnancy tensile strength did not differ from tensile strength in a control group of non-pregnant rats, indicating that the stimulation of healing during pregnancy is due to some factor referable to the first third of pregnancy.

The possibility of endocrine stimulation of healing during the early phase of pregnancy is discussed.

The importance of the endocrine influence on the healing processes during pregnancy is not clarified. Clinical observations on pregnant women seem to support the hypothesis that tissue formation is stimulated, e.g. in the gingiva and in the mammary glands. Collagen formation is increased both in the uterus of the rat and in the human uterus during pregnancy (Harkness & Harkness, 1954, Morrione & Seifter 1962). Studies of the influence of pregnancy upon healing in animals are not unanimous (Localio & Chassin, 1952; Kullander & Olsson, 1962). Clinical observations of the tendency to keloid formation in scars during pregnancy and of the beneficial effect of pregnancy upon peptic ulcer (Sandweiss et al., 1938), give further support to the notion that endocrine factors are of importance to healing during pregnancy.

The present study was started in order to investigate, if the rate of collagen formation in rapidly growing tissues in other sites than in the uterus was stimulated during pregnancy in the rat, and if this was found to be the case, to investigate, if it resulted in improved healing.

The capacity of forming collagen in subcutaneous sponge implants was studied on a group of rats before pregnancy and during a certain phase of the pregnancy

LOCAL TREATMENT WITH ANTIBIOTICS IN CASES OF MAXILLARY SINUITIS

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In the treatment of empyema in the maxillary sinus different preparations with sulfa or antibiotics have in the last 20 years been instilled after rinsing out the pus. Over 1500 empyemas have been treated. In the last 5 years only erythromycin-Abbott mixture has been used on a patient material comprising 811 maxillary sinuses. Of these 55 per cent (459 cases) have healed up with one rinsing and 82 per cent (691 cases) with at the most two rinsings. Sinuses that have been rinsed more than twice have as a rule been endonasally trepanned according to Ostrom (17% or 141 cases). In only 2 cases (0.1) has radical operation according to Caldwell Luc been necessary. Erythromycin-Abbott mixture which has a tolerable taste has proved to be a suitable preparation for instillation in the maxillary sinus. No allergic or other side-effects have occurred in this material

St. Clair Thomson and Negus (1916) have advanced the following aims for the local treatment of an empyema in the maxillary sinus.

1. To facilitate drainage
2. To arrest growth of bacteria.
3. To soothe pain.
4. To control blood-stream infection.
5. To avoid complications.

To these Strong and Tonkin (19.1) add.

6. To reduce period of convalescence and prevent recidivation.

To which I should further like to add.

7. To restore the normal bacterial flora of the nose, which is completely dominated by Staph albus and Corynebacterium (Björkwall, 19.0).
8. To create aerobic conditions in both sinus and nasal cavity

The last point 8., covers in itself all the other seven points. Caldera and Santi (1919) plugged healthy nasal cavities and were able, after only 12 hours, to find virulent anaerobia in the nose while at the same time they found that Staph albus and Corynebacterium had been decreased or had disappeared.

Earlier Investigations

Sulfanilamide was used by Childrey (1939) and Silcox and Schenk (1912). I myself tried *prontosil* as early as 1941 while Richtnér (1912) and Everett give an account of *sulfathiazole* (1916) *Penicillin* was introduced by Sale and Diamond (1944) and by Priest (1945) Forman (1917) and Walford (1919) leave the cannula or a urethral catheter in the sinus for some days in order to be able to rinse out

the sinus with a penicillin solution several times a day with less discomfort for the patient *Streptomycin* began to be used by Fineberg (1948) and the following year (1949) a report on *penicillin-hyaluronidase* was submitted by Som et al. In a lecture in the Norwegian Oto-laryngological Association on December 13th 1937 Gording gave an account of his own experience of local penicillin therapy mentioning in this connection Herrell's (1945) and Simpson's (1946) experiments with the same treatment Also van Hoorde (1949) used penicillin.

A detailed study of *procaine penicillin-in-oil* therapy was published by Strong and Tonkin (1951) At the same time they described the effect of the penicillin upon the ciliary activity Two years later (1953) van de Loo published the ex per iences gained with *penicillin-novocain-oil suspension*, which in very large series has also been used by Bachman (1960), who however has subsequently abandoned this form of therapy and who recommends instead the use of *Tacho-liquin foam* with simultaneous parenteral supply of penicillin. Tacholiquin is a secretomucolytic agent.

In subsequent years (1953—1954) Nielsen, Poulsen and Blegvad and Decher (1957) published their experiments with *Nebacetin* and Elsen his experiences with *penicillin G procaine* (1955) In this work Elsen draws attention to Alyea's critical attitude to local treatment of sinus.

Swik used »*Didrosulfon-gel*» (water-soluble sulfonamide-Aristamide Z and dihydrostreptomycin) (1956). About the same year (1955) Flechsig began to touse *Terramycin* locally in sinus, which also Schöler (1956) and Brasche (1957) have preferred. Brasche introduced *terracortril-salve* (oxytetracyclin with hydrocortisone) and used also *terracortril eye suspension* (terramycin-polymyxin B-hydrocortisone) Also Strandbygaard (1965) Szöke and Horvath (1960) used *oxytetracyclin* which, plus *polymyxin*, is also proposed by Barefoot (1962).

Different antibiotics together with *alpha-chymotrypsin* have been used by Dobbelbeer (1961) and by Szpunar together with *hydro-cortisone* (1962). Decroix and Deguines (1963) have used *rifamycin*, a product of Streptomyces mediterranei. Czigany (1963) suggests a »*cocktail of polymyxin B-neomycin and dexamethason* (fluormethylprednisolon F 6)».

Simultaneous parenteral and *local penicillin water solution* has been tried by Kortekangas (1964).

Mutschelknauss (1964), finally has in a critical study given an account of the advantages of local treatment with *terracortril-gel*

As has emerged from the works reviewed above, about twenty different antibiotics and chemotherapeutic agents have been instilled in sinus after the usual maxillary rinse. The preparations have been different physical suspensions, gel-preparations, salves. Some of the pure preparations have been used by themselves or in mixtures with or without steroids, sometimes with agents reducing surface tension.

The general impression is that *oil-suspensions and gel preparations* have given the best results (Strong and Tonkin, van de Loo, Elsen, Mutschelknauss). Less successful results have been obtained with *water solutions*. Gording, Priest, Putney Dunn, van Alyea, Boies, Morrison, Kortekangas) In different experi-

ments it has proved that the oil-suspensions do not liberate free penicillin as rapidly as do water solutions. In this way the deleterious effect that high penicillin concentrations have had on the ciliary activity has been avoided (Strong and Tonkin Elsen)

A number of writers have been of the opinion that antibiotics in general are not at all resorbed by either the healthy or the inflamed mucous membrane in sinus. This hypothesis has been based upon the assertion that pus and mucus produced by the mucous membrane prove that the traffic runs in the opposite direction. These all too loose assertions have been refuted by different writers, who have shown that the resorption through the mucous membrane to the blood (Strong and Tonkin)

The *parenteral supply* of antibiotics has in general shown very poor results in the treatment of sinuites without any other form of therapy being undertaken at the same time. Elsen Kortekangas, Mutschel-Knauss. In the case of complications from sinus and when simultaneous conservative (rinsing) or surgical treatment has been undertaken parenteral treatment has been recommended (Bachman)

It is probable that quite a number of other antibiotics and chemotherapeutic agents have been tried in sinus, but these are at the moment not known to me Erythromycin has not previously been used in this connection.

Acute and chronic sinuites

An empyema in the maxillary sinus was earlier in the first place regarded as a surgical condition, and it was treated accordingly with rinsing of the sinus, endonasal trepanation or radical operation. These forms of therapy were then as a rule preceded by or combined with the usual traditional treatment with warmth VHF nose drops, camomile vapour treatment (in Germany) or nasal suction according to Proetz, which is common in Denmark.

In the literature reviewed above no writer has defined his attitude to the acute and chronic condition. It may therefore be worth while pointing out that an acute inflammation of the mucuous membrane of the maxillary sinus is a reversible process. After the inflammation, whatever the cause may be the normal appearance and physiology of the mucous membrane is restored

In the case of a chronic inflammation of the mucous membrane this is an irreversible process, where the histopathology is the same whatever we do (Kutner 1931 Jensen 1933, Heerup and Kettel 1937) A chronic inflammation of the mucous membrane means as a rule a simultaneous fibrous change.

The question of a chronic sinuitis can thus not be put by the doctor engaged in treating the patient whether he has rinsed 9 or 39 or 112 times. He must take the trouble to arrive at a pathoanatomic diagnosis if he is to have a correct diagnosis. The question is thus not clinico-bacteriologic, but histopathologic. This is unfortunately only too frequently forgotten when one has become tired of rinsing and hastens to perform a radical operation.

Thus in the light of the above one should at the very first acute sinuitis in one's patient always bear in mind that the inflammation must be checked as soon as

possible — and this in view of the fact that the mucous membrane must not be given the possibility of being exposed to a fibrous change in connection with protracted treatments and recidivations.

As was pointed out in the introduction, one should try as soon as possible to get the maxillary sinus sterile and to create aerobic conditions in the nose. This is achieved most quickly with maxillary rinsing and simultaneous local antibiotic treatment of sinus, preferably with a wide-spectrum antibiotic with bactericidal effect. The resorption through the sinus mucous membrane should take place slowly an the preparation should remain in the maxillary sinus as long as possible. There should be no deleterious effect on the ciliary activity. No parenteral antibiotic therapy should be undertaken in connection with this routine treatment.

Author's own observations of local therapy

In previous years I have used prontosil, sulfonamide, chloromycetin-palmitate, sulfanilamide penicillin-sulfa mixtures, various penicillin suspensions aureomycin and terramycin with or without hydrocortisone. These treatments have not been more closely followed up, only practical conclusions have been drawn from case to case. In the course of the years the number of these observations has amounted to 755. There have never been any allergic symptoms.

Own observations with erythromycin-Abbott

In the treatment of empyema in the maxillary sinus erythromycin-Abbott in preparations for oral administration has been used for the past five years. It has been used in the form of a 4 per cent mixture a 2 per cent mixture and as a granulate for suspension in water. Erythromycin was chosen because it has a bactericidal effect on pneumococci, streptococci, staphylococcus aureus and also Haemophilus influenzae. These bacteria occur in the order mentioned chiefly in cases of acute and chronic sinuites (Björkwall 1950, Nielsen 1957). Erythromycin has no deleterious effect upon the ciliary activity (Sylvester 1960) and side-effects — including allergic effects — occur very seldom. There are no toxic effects on the blood, the nervous system, liver or kidneys, nor is there any discoloration of the dental enamel. The decisive criteria applied to the results of treatment have in this investigation been only the clinical picture, the patient's freedom from symptoms and the appearance of the rinsing fluid.

Technique

After the usual maxillary rinsing 2 ml erythromycin mixture (4% or 2 %) has been injected into the maxillary sinus through the indwelling cannula while the patient has at the same time leaned his head to the affected side. When the granulate has been used about 1 teaspoonful of granulate (5 g) has been added to 10 ml sterile water and stirred with a sterile ear-stick in a sterile stainless steel bowl. Of this, 5 ml has been drawn into a sterile syringe for instillation in the maxillary sinus in question. A further rinsing has always been performed after

48 hours, only in a few cases after 24 hours or after 3—4 days on account of holidays or for other reasons

Remains of erythromycin mixture (red colour) have been regularly observed in the sinus at the subsequent rinsing In this connection one ought perhaps to remind oneself of Törne s (1902) observations of the ciliary activity where even 64 years ago he showed that a foreign body introduced into the maxillary sinus can as a rule still be shown to be present after 78 hours.

RESULTS

No difference in the results due to which erythromycin preparation was used have been observed

Since the rinsing frequency is practically speaking the criterion by which the doctor judges the case and frequently the indications for operation (van de Loo Elsen, Scholer Mutschelknauss, Bachman) the table below has been drawn up with this in mind.

The number of patients treated amounted to 512, and the number of affected maxillary sinuses (cases) among these 811 In 25 cases the rinsing water had a strong fetid smell at the first rinsing In 20 patients (4 %) dental granuloma was observed roentgenologically and in 47 patients (9) a marked septum deviation.

TABLE 1

P+++ = VERY LIQUID PUS, P++ = MUCOPUS, P+ = ISOLATED CLUMPS

Number of rinsings	P+++	P++	P+	%	Number of maxillary sinuses
1	4	3	43	6 %	50
2	121	225	65	49 %	409
3	106	110	10	27 %	232
4	56	34	2	11] %	93
5	31	11	—	5 %	42
6	9	2	—	1.3 %	11
7	6	—	—	0.6 %	5
Total	332	301	118	99.9 %	811
Endonasal trepannings	99	40	2	17 %	141
Radical op accord. t C-L.	2	—	—	0.1 %	2

It will be seen that the above table has been drawn up with reference to the number of rinsings for each sinuitis, and the last rinsing has always shown *clear* rinsing water [cf Elsen, van de Loo Swik Schöler] This means that 691 (6 %+49 %+27 % = 82 %) maxillary sinuses healed up after two rinsings and two instillations of erythromycin, while 459 cases (6 % +49 % = 55 %) healed up with a single treatment.

In the light of the aims of the treatment set forth in the introduction endonasal trepanation has as a rule been undertaken if the third rinsing has still shown pus. A small number of cases in which the patients would not agree to an endonasal trepanation were rinsed more than three times (1 %). The rest, or 17 per cent,

were endonasally trepanned with Ostrom's instrumentarium, which seems to me sure and easy to work with. Inspection in the endonasal fenestra has always been made after the operation. A 5 cm broad adrenalin-soaked tampon has been placed in the fenestra after the operation which has been performed policlinically. The following day the tampon has been carefully removed.

Control rinsings of these 141 endonasally trepanned cases have been performed one week later and in no case has the rinsing water shown pus. The rapid healing is ascribed to the aerobic milieu to which the mucous membrane of the maxillary sinus is exposed as soon as one lets air into the sinus (Leiri 1939, Nielsen 1957, Blegvad 1957). In those cases in which roentgen control has been made before and after the treatment a clearing up of the ethmoidal regions and the frontal sinus has been observed.

Only two cases of 841 sinuites have called for radical operation according to Caldwell-Luc. The same observations have been made by Mutschelknauss (1964), van de Loo (1953), Schöler (1956).

The results of instilling erythromycin mixture after rinsing of the maxillary sinus agree with and excel the earlier observations with antibiotic oil suspensions (Strong and Tonkin 10.1, van de Loo 1953, Elsen 1955, Swik 1956, Brasche 1957, Szpunar 1962, Czigany 1963, Mutschelknauss 1964).

CONTROL MATERIAL

Rinsing of sinus w i t h o u t *local treatment with antibiotics*

In the course of earlier examinations (1950) the author rinsed 38 maxillary sinuses (acute sinuites) repeatedly until they had healed up or a surgical operation was performed, which was done in 14 cases.

In 7 cases (18%) the inflammation was healed with 2 rinsings, in 9 cases (21%) with 3 rinsings, in 4 cases (10%) with 4 rinsings and in 2 cases with 5 rinsings. A number of maxillary sinuses were rinsed 9, 13 and 18 times before they were operated on.

The following results emerge from a comparison of this series *without* local treatment with antibiotics with the material *with* local treatment with antibiotics described in this work.

It should be observed in this connection that *at least* means that the patient has been rinsed once more than is indicated in the table, since the last rinsing in both series has shown a clear rinsing fluid.

TABLE 2

THE HEALING TENDENCY WITH REFERENCE TO THE FREQUENCY OF THE SINUS RINSINGS

	At least 1 rinsing	At least 2 rinsings	At least 3 rinsings
Rinsing without treatment with antibiotics	18 %	(18+21 %) 42 %	(18+21+10 %) 52 %
Rinsing + local erythromycin instillation	(6+49 %) 55 %	(55+27 %) 82 %	(55+27+11 %) 93 %

Despite the fact that the control material is small, it establishes statistically the tendency which in this respect it is desired to attain. It emerges from the table that local treatment with antibiotics (in this work instillation of erythromycin mixture Abbott) is clearly superior to the conservative form of treatment without instillation of antibiotics. In uncomplicated sinuites the healing tendency is twice as great (the frequency sinks to the half) with local instillation of erythromycin in connection with rinsing as compared with maxillary rinsing without instillation of antibiotic

I wish to convey to H Hasselqvist, Head of the Information Dept Malmö Dr J hn C. Sylvester Chicago and J O Lundberg M.A., Södertälje for their kind assistance

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DISCUSSION

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In the last 4 years I have done very few antral punctures except by sinuitis dentogenica. My standard treatment have been a Proetz displacement therapy combined with nasal drops, and in a few cases with antibiotics per os too.

It is very essential to fill the nasal cavity completely with ephedrine solution by the Proetz displacement therapy.

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THE CHRONIC EAR. OPERATIVE METHODS AND RESULTS

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During th 2 year period of 1964—1965, 303 chronic ears were operated at the Oulu Clinic. In 70 cases myringoplasty or tympanoplasty was made without mastoid bone work, and in 233 cases the radical bone removal was included. For repair of the drum and part of the meatus, temporal muscle fascia was used exclu sively and the cavity was occluded with the musculoperiosteal pedicle flap as advocated earlier Certain important phases of the tympanic repair are elaborated and results in various clinical subgroups presented.

The period of the open radical mastoid cavities started in the 1890-es and with routine skin grafting lasted about 70 years. A number of efforts had been made meanwhile to get rid of the cavity but these did not involve simultaneous repair of the drum Even though some of these methods included ideas, still up-to-date at present, none of them gained sufficient support to become a routine procedure.

In 1957 Unterberger placed temporal muscle fascia under split thickness skin grafts for repair of a tympanic perforation. In the same year Zangemeister used fascia for sealing the oval window in otosclerosis surgery and in 1960 we also began to employ it (Meurman and Palva 1962) However Shea had already earlier used vein for the same purpose, and when he extended the use of vein grafting to the repair of tympanic perforations (Shea 1960 Austin and Shea 1961), placing the plain vein under the drum margins, this provided a clue as to how to convert the radical operation into the present method of fascio-meato-tympanoplasty with cavity obliteration (T Palva 1962)· the drum is repaired with temporal muscle fascia which — together with the posterior musculoperiosteal flap obliterating the cavity — is utilized for reconstructing the external ear canal. No skin grafting is used, initially longitudinal incisions were employed in the ear canal, but now this latter is conscientiously kept as a closed tube.

Figure 1 shows a schematic view of the formation of the musculoperiosteal flap. In cases of small sclerotic mastoid processes with few pneumatic cells the cavity becomes small, and the flap need not be large. If, however the cavity appears to become extensive, the flap should be broad and long to provide substantial material for obliteration. Postoperatively the flap swells and generally occupies one and a half times as large a space as during surgery Therefore, if the flap initially is too large for the cavity and the posterior bony canal wall is removed swelling may cause a temporary narrowing of the ear canal.

In most cases, the cavity is well obliterated with this flap; it may need a small piece of neomycin-soaked gelfoam behind it for better fixation. In about 5 per cent of all cases the cavity becomes so extensive, the volume exceeding 5 cc, that it is advisable to fill the empty space with inorganic bone (Ossar®).

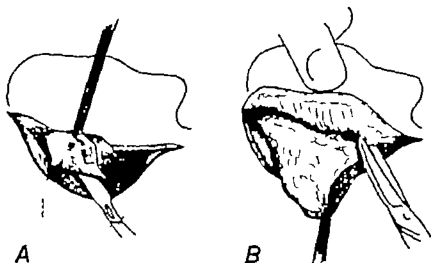


Fig. 1 Schematic presentation on the formation of the musculoperiosteal flap. Initial liberation of the flap posteriorly (A). Liberation of the flap anteriorly (B).

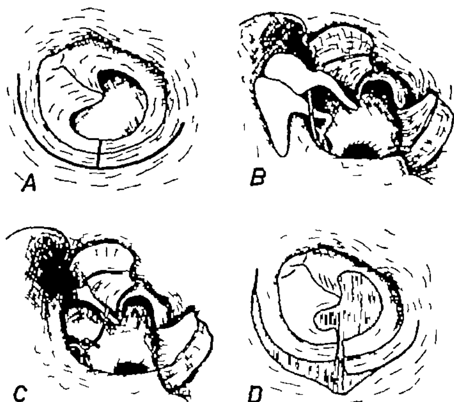


Fig. 2. Schematic presentation of the operative procedure in tympanic reconstruction in cases with partial pars tensa defect. An incision is made 5—8 mm above the annulus in a swing-door fashion (A). The skin flaps are reflected and the malleus handle denuded and the free edge of the perforation refreshed. The ossicles are preserved (B). Incus and head of the malleus may be removed, and a stainless steel wire prosthesis is used to connect the malleus handle and the stapes (C). Fascial graft in place under the drum remnant, over the malleus handle and under the meatal skin (D).

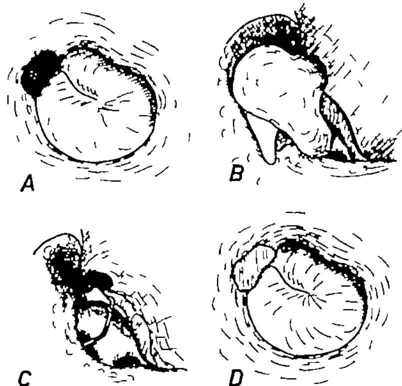


Fig. 3. Operative procedure in epitympanic perforations. The epitympanic defect as seen by the surgeon (A). The ear canal skin is reflected forward exposing the cholesteatoma sac (B). The cholesteatoma, incus, and head f malleus are removed, with exposure of tympanum. Ossicular reconstruction is made from the malleus handle to the footplat (C). Fascial graft in place closing the epitympanum (D).

Before starting the drilling, the incision must liberate the auricle both superiorly and inferiorly so that the ear canal skin can be folded forward as an intact tube. This also offers the surgeon an excellent view into the tympanum, the window niches and the facial sinus, which, if viewed from a more posterior angle, are not seen well enough

In drilling of the cavity the main task is to remove the cells, which generally contain serous fluid, cholesterin cysts, granulations or collagen. If the mastoid consists of ivory hard bone we do not insist on enlarging the cavity to the sigmoid lamina and mastoid tip provided there are no cellular tracks leading there. Bacterial specimens and tissue cultures from the vicinity of the antrum have shown no growth in 80 per cent of the cases, and the more distal cell tracks have been sterile almost without exception. In obliteration, one thus does not bury the infection even if some connective tissue containing cell tracks may be left behind the labyrinthine block or deep under the facial nerve.

In cases with well limited cholesteatomata the obliteration operation is simple: it should only be kept in mind that removal of the matrix does not mark the end of mastoid bone work, which must be as thorough as on any other occasion and

Fig. 4. Photographs f various types of reconstruction. Partial pars tensa defects: A tainless steel wire connects the malleus handle to the arch of the stapes (A). A wire prosthesis between the malleus handle and the footplate (B). Total pars tensa defects with no malleus: A two-leg wire prosthesis round the stapes (C). A three-leg wire prosthesis with no stapes superstructure. One leg lies on the footplate and the others are in the a terior part of the tympanum.

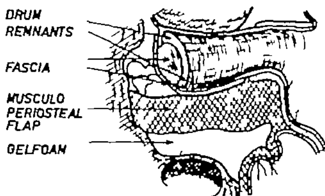


Fig. 5. A horizontal section of the total procedure with meatal reconstruction and cavity obliteration. In radical ear surgery any one of th tympanic reconstructions depicted in figs. 1—4 can be combined with this procedure.

include all bone up to the healthy sigmoid and dural laminae and mastoid tip If there is an invasive cholesteatoma, the keratinizing squamous epithelium filling cell after cell without limiting matrix, the problem is more serious. We obliterate the cavity if one can follow the cell tracks under the microscope and finally encounters only healthy bone. This may present difficulties, particularly around the semicircular canals, and only highly experienced surgeons may in these cases obliterate the cavity In doubtful cases, the ear canal should be enlarged and only the safe part of the cavity occluded.

When making an obliteration operation with creation of a new ear canal in old open cavities, it has been necessary to remove much diseased bone with unopened cells. Once the skin lining has broken down, there has been no end for the discharge until appropriate bone work is done afresh. We have been rather disturbed by the frequency of incompetent surgery sometimes even by trained specialists.

In teaching hospitals, particularly those with much resident surgery there should be at least one qualified permanent staff member who supervises each ear operation. Only by proper training, and by demanding perfect technique can the general standard be expected to rise so much as to give safe ears as a result.

The tympanic part of chronic ear surgery may be very easy or may be extremely difficult, forcing even an experienced operator to leave the tympanum unreconstructed, particularly when cholesteatomatous material fills the whole tympanum and the Eustachian tube. It is then not possible to drill away the underlining bone in the same way as in the mastoid area, and the chances of leaving microscopic cholesteatomatous rests are much more real.

Repair of the drum is made essentially along the same lines in all cases, viz. by placing the fascial graft under the refreshed margins of the drum In total perforations the fascia is placed over the meatal bone and covered with meatal skin. Reconstruction of the sound conduction system necessitates the use of different methods, and we use the following three procedures. (1) the ossicular chain is left intact or is reconstructed (2) columellization is made (3) no reconstruction is made. We have abandoned the use of window plasty and have not used fenestration of the horizontal canal. In some cases there may be room for the latter but even so the oval window route with columellization should prove possible.

We prefer to repair the drum defect in the form of a tympanoplasty by raising the swing door flaps that enable us to have a look into the window regions, and if required, into the attic. We mostly use the endaural route. If there is an anterior perforation with a forward sloping ear canal, then a postauricular incision gives a better exposure.

In performing the radical mastoid operation, in cases of cholesteatoma, we always remove the bridge at the tympanic area so as to have a full exposure of the attic. If the matrix can be teased away from the external surface of the ossicles easily these have been spared. If the matrix extends deeper the incus and head of the malleus are removed we presently employ a wire prosthesis from the malleus handle to the stapes arch or if the superstructure is missing, directly on the foot plate. If epitympanic cholesteatomata are diagnosed early and operated upon, the tympanum is often intact, and the chances of good postoperative hearing are ex

cellent. If operation is made in the late stage, extensive involvement of the tympanic cavity by cholesteatoma greatly reduces the chances of hearing improvement.

In the absence of macroscopic cholesteatoma and if disease at the antral area is minimal, we retain a thin bridge and make the usual swing door reconstruction. If the ossicles are extensively involved by fibrous tissue and granulations, the bridge is removed and the attic cleaned. If the chain is mobile we leave it in place; if not the incus and head of the malleus are removed and reconstruction is made from the malleus handle with a stainless steel wire. The great majority of our cases show *extensive osteitis, the bridge is then carefully removed, the facial nerve followed* the cells lateral to it removed and the facial sinus cleared.

Most of our cases with pars tensa defects displayed an extensive involvement of the promontory mucosa. We felt it was necessary to make a total clean-up of the tympanic cleft, leaving only periosteal islands here and there. If the pars tensa and the malleus handle were destroyed we formed a wire prosthesis with one »leg» in the Eustachian tube orifice another in the hypotympanum, and a third on the footplate or the stapes arch being intact round the stapes head. Owing to poor Eustachian tube function, there is a great tendency for an adhesive middle ear to develop. For its prevention, we are now experimenting with a Silastic sheeting over the denuded promontory or we purposely leave an anterior perforation for permanent aeration of the tympanum via the meatus.

With a view to permanently improved hearing, poor function of the Eustachian tube presents the most difficult problems in chronic ear surgery. It seems to us that if the tube cannot be made to function properly viz. if it does not allow air to enter the tympanum on each act of swallowing, then absorption is certain to occur and long term hearing results are not good.

During the two years (1964—65) of the existence of the Oulu University ENT Clinic we have performed 303 ear operations, which can be grouped as follows.

1) Tympanoplasty with preserved or reconstructed ossicular chain without radical surgery	70
2) Same with radical surgery	54
3) Columellization with radical surgery stapes present	83
4) Same without stapes superstructure	43
5) No reconstruction	35
6) Preoperatively deaf ears	18
Total	303

Of these 303 ears, only 80 were completely dry preoperatively. In addition, bacterial cultures were negative in 39 before surgery. The most frequent invader was *pseudomonas pyocyaneus occurring in 57 ears, followed by yellow staphylococci* in 37 ears and proteus strains in 22 ears. Postoperatively there was discharge for some time, generally a few weeks, in 31 instances, but only 2 of the ears were discharging continuously. Postoperative drainage during the early period was to be expected considering that in 35 cases no reconstruction of the tympanum was made; it always takes some time before the cleft is epithelialized again.

A more thorough analysis of the hearing results as related to various types of prostheses will be presented later tympanoplasties with an intact mucosa yielded the best results, and practical hearing was present postoperatively in 90 per cent With a preserved chain but with radical bone surgery and diseased tympanum, the percentage dropped to about 50. Columellization in this series still without wire prostheses and mainly with a polyethylene tube on the stapes superstructure or on the footplate, resulted in practically useful hearing in about 35 per cent the total material

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MASTOIDECTOMY WITH MUSCULAR OBLITERATION MODIFIED AFTER PALVA

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In Aalborg — during 20 months — 93 cases of simple and radical mastoidectomy have been done for acut and chronic otitis media. In the material the chronic cases dominate especially the very chronic.

Totally 43 simple and 50 radical mastoidectomies of varying radicality have been made cholesteatoma was found in 31 cases (33 %), fistula of the external canal in 11 cases (12 %) and in 52 cases (56 %) the ossicular chain was found interrupted most often by ostitic destruction of crus longum incudis

Great care has been made to remove ostitic bone as thoroughly as possible. I all but 3 cases a muscle obliteration of the cavity has been done. In 83 cases was used a retroauricular muscle flap a little modified after Palva s method. In 3 cases an anteriorly based flap from the temporal muscle and in 4 cases a combination of different muscle flaps were used. The material was evaluated 1—22 months after the operation. It is concluded that muscle oblit ration of the cavity after Palva is an easy and technically attractive method in order to obtain a complet or partial obliteration of the cavity Th muscle flap is broadly based, always viable and little bleeding. In no case necrosis or pocket of infection have developed, and the post operative reactions have been minimal. The imple mastoidectomies almost all have healed up quickly and neatly and two thirds of th radical cavities have be come dry and covered by epithelium. As a whole the methods has given fine results.

However the retroauricular muscle flap seldom will fill out more than half of the cavity On the medial side of the flap granulation tissue often forms, delaying the final healing. A definite drawback with the method is its weakening of the cover f soft parts over the retroauricular often very big cavity Even if we have not had lasting retroauricular fistulae the thin cover has been suspicious in some cases.

In July 1964 when the Ear Nose and Throat Department in Aalborg opened it soon became obvious that there were a great number of cases of chronic otitis media in the district who would seek the department in the coming years for operative treatment. Very chronic and very deep processes would have to be anticipated The problem was to establish an operative procedure which would arrest the ostitic process effectively and thus remove the risk of complications. The post operative course should be as rapid and free from complications as possible. On the other hand less attention would be paid to the possibility of obtaining increase in hearing by means of primary tympanoplastic interventions as it was to be anticipated that grossly infected discharging ears would be involved and that the patients concerned had become accustomed to a useless ear over a period of years.

Interest was naturally concentrated on a muscle obliterating procedure From healthy surgical principles, it is considered attractive to introduce a pediculated muscle flap into the resection cavity so that this would not only obliterate the



Fig. 1 Left Palva' method. Right. Present a thor' method.

cavity but also, on account of its good vascularity it would bring increased possibilities for resistance and regeneration to the devitalised walls of the cavity The system of obliteration with a muscle flap has been recognised for many years but was not employed to any great extent until introduction of antibiotics. Rambo (1957) thus employed a flap from the temporalis muscle with an anterior pedicle and later duplicated this in order to reach the apical part of the cavity The flap may be made in approximately the size desired but will always be rather narrow at the base and show a certain tendency to be constricted where it traverses the edge of the cavity Guilford and his co-workers (1958) employed a flap with an inferior pedicle from the sterno-cleido-mastoid muscle. This flap may also be made quite large and can be supplemented with a flap from the temporal muscle if the cavity is large

Palva has employed a muscle flap consisting of the retroauricular muscle with surrounding fascial tissue routinely since 1957 (Palva 1962 and later). Palva s method includes primarily partial or complete obliteration of the mastoidectomy cavity with the retroauricular muscle but, in addition, closure of the inner part of the cavity with a fascial flap from the temporal muscle which is introduced under the remnants of the tympanic membrane and is placed directly upon the muscle flap

Employment of the retroauricular muscle is tempting for many reasons. It is rapid and easy to free, it has a broad base and a good vascular supply Admittedly it may vary considerably in size but always suffices to provide a solid muscle-connective tissue plaque. Detachment should not extend too far posteriorly as troublesome haemorrhage from the emissary vein may result. Palva s retroauricular muscle flap has the advantage over the two others that it does not adhere so closely to the medial wall of the cavity that there is a risk of formation of loculi. In Palva s hands, this method has produced extraordinarily good results with only 5 per cent discharging cavities out of more than 400 cases submitted to operation (Palva 1965).

Although complete extripation of all pathological tissue is aimed at, it must be recognized in practice, however that complete extirpation is not possible in all cases. Microscopic foci of infection may remain and, occasionally more serious secondary complications have been described and attributed to incapsulation of foci of infection behind the large muscle flaps or behind fascial closures (Elbrond (1962), Junge Pedersen (1962) Palva (1962)).

The present author has, therefore elected to employ Palva s procedure with, however the modification that no attempt is made to close the little residual

cavity in connection with the meatus. Instead an attempt is made to form the little residual cavity corresponding to the antrum and the cupular space into a smooth-walled extension of the meatus while the retroauricular muscle flap fills the lateral and largest part of the cavity directly covered by skin from the meatus. In suitable cases, particularly where the pars tensa remains more or less intact it has proved possible to shut off the middle ear from the meatus by means of a thick Thiersch graft. This method represents a deviation from Palva s method and the same good result as regards persistent secretion cannot, therefore be anticipated. On the other hand the modification introduced is considered to have reduced the risk of infective complications in the entire closed cavity

As both ears were submitted to operation in two patients and one ear was re-explored 93 operations were concerned, carried out on 92 ears in 90 patients. Of the ears concerned 56 were in males and 36 in females. In 51 cases, the right ear was involved and in 41 cases the left ear. The youngest patient was eight months and the oldest 70 years, the average being 31 years.

In the majority of cases, pronounced chronic otitis was concerned which in many cases, had been present for a lifetime albeit with relatively symptomless periods. The first occurrence was frequently in early childhood. In 11 cases only the disease had been present for less than one year. In 36 cases, or more than a third of the material, the disease had been present for more than twenty years, and a not inconsiderable number of patients had lived nearly all of their lives with an inflammatory process in the ear

No detailed description of the symptoms will be given here but special conditions will be pointed out which illustrate the nature of the material to a particular extent. Table 1 demonstrates schematically the incidence of a series of important symptoms and complications. Although the reduction of hearing can practically always be demonstrated the patients seldom complain of this, provided the other ear is healthy

In practically all of the cases a retroauricular incision was employed. The actual mastoidectomy was carried out in the traditional manner great emphasis being placed on as complete excavation as possible of the ostitic foci. For various reasons muscle obliteration was not done in 3 cases only. Thiersch grafts were

TABLE 1

FREQUENCY OF CERTAIN SYMPTOMS. NUMBER OF CASES

	Existent	Absent	No Information
Discharge	90	2	
Pain in ear	51	32	10
Vertigo	28	48	17
Gustatory disturbance (monosymptomatic)	1		
Syndroma of Gradenigo	1		
Acute Meningitis	4		
Facial palsy	2		
Other neurological symptoms mostly headache	23		
Spontaneous nystagmus	4		

employed for covering large raw bone surfaces and where it proved possible to shut off the middle ear in 25 cases.

Operative and post-operative complications were few Pyrexia of 38°C (100.4°F) was quite common on the first day In one case only pyrexia suggesting sepsis occurred for 4—5 days. As sinus phlebitis was suspected, re-operation was under taken but no residual focus was encountered and the sinus was normal. In one case where the dura was covered by granulations, severe neurological symptoms occurred ten days after operation. A temporal lobe abscess was found and evacuated in the Neurosurgical Department and recovery ensued. In one case moderate perichondritis caused prolonged trouble In the remaining cases, primary healing took place rapidly and easily and, in particular there were no signs of reduced vitality or necrosis of the muscle flap introduced and no loculi of secretion were observed behind the flap

The retroauricular scar healed rapidly and well in practically all cases and no persistent fistulae occurred. The thin soft tissue covering over the cavity resulting from formation of the muscle flap however caused trepidations as to whether the scar would hold in a number of cases. It appears to be important that the incision is firmly closed with through-and-through mattress or deep subcutaneous sutures. In nearly all of the cases, the auditory meatus retained its normal width.

On control examination from 1—22 months after operation, a lesser saucer shaped cavity was found medial to the flap posterior to the spur and the meatus was of normal appearance. The cavity was entirely obliterated by the muscle flap in only a minority of cases. On comparing the estimated size of the muscle flap during operation and at control examination, the impression is formed that the retroauricular muscle flap shrinks moderately It is the author s most definite impression, however that the flap retains its vitality well and that it becomes adherent to the osseous walls with which it comes into contact. In an isolated case where re-operation was undertaken five weeks after simple mastoidectomy the fibres of the retroauricular muscle were found to be fibrously adherent to the walls of the cavity and to be fully viable and capable of functioning

Practically all of the ears were dry or without secretion of note on discharge from hospital. The impression was gained clinically however that in some cases secretion recurs from the cavity after some months have elapsed. As a rule, it is possible to get these ears dry again by means of various forms of local therapy Quite often there is granulation formation on the medial aspect of the muscular flap or on the spur and when this is removed, the ear dries up as a rule. A total of 68 per cent of the ears submitted to operation were found to be completely dry on follow-up examination. Ears with slight discharge appear to dry up gradually and may therefore, be included in the group of quite good ears which thus comprizes 85 per cent satisfactory ears. The two last groups of 15 per cent altogether comprize cases of simple mastoidectomy with secretion and cases with radical operation and genuine secretion. This total of 13 ears must be considered as unsatisfactory 6 ears, however were by a later examination found to be without discharge.

Four patients defaulted from follow-up examination The ears involved were completely satisfactory on discharge from hospital.

If the material is subdivided according to the nature of the operative intervention undertaken, it is observed as might be anticipated, that simple mastoidectomy yields slightly better results than the radical operations as the acute operations without such deep ostitic processes are classified in the group of simple chisellings. 90 per cent of the simple mastoidectomy fall into the satisfactory group while only 82 per cent of the ears submitted to radical operation were dry or nearly dry. Further it is observed that the various forms of primary tympanoplastic procedures do not appear to compromise the results. Table 2.

TABLE 2

RESULTS OF VARIOUS FORMS OF SURGERY. NUMBER OF CASES

	Excellent. Ears completely dry	Satisfactory	Unsatisfactory	No information
Simple mastoidectomy without tympanoplastic procedures	31	1	4	3
Simple mastoidectomy with tympanoplastic procedures	3			
All simple mastoidect.	34 ~ 87.2	1 ~ 2.6	4 ~ 10.2 %	
Radical mastoidectomy without tympanoplastic procedures	11	14	6	1
Radical mastoidectomy with tympanoplastic procedures	13	2	3	
All radical mastoidect.	24 ~ 49.0 %	16 ~ 32.6	9 ~ 18.4	

Further investigation of the conditions prevailing in the nine unsatisfactory cases submitted to radical operation revealed that, in the patients concerned growths of proteus, pyocyaneus and gram-negative rods which were not identified further were found strikingly frequently i.e. in 8 cases.

There seem to be reasons to consider infection with proteus and pyocyaneus as being more serious particularly if complicating conditions are present or conditions which involve local or general reduction of tissue vitality. A special pre-operative treatment plan will be introduced for patients with these infections.

On the other hand, the age of the patient at operation does not appear to play any special role. The presence of cholesteatoma does not appear to predispose to a poor result either. A muscle flap was introduced in all of the nine cases mentioned and the continued secretion was not considered to be attributable to this in any of them.

Out of the four cases of simple mastoidectomy which were still discharging, three had only slight discharge and had been observed for from 3 to 6 months only. These cases will probably dry up later. The fourth patient was a mentally retarded patient from an institution. No particular preponderance of proteus and pyocyaneus was encountered in these cases.

In the cases of simple mastoidectomy hearing deteriorated by an average of 5 db as compared with the pre-operative hearing with quite considerable scatter to both sides. The cases of radical mastoidectomy without tympanoplastic pro-

cedures are distributed with approximately as many above and below the preoperative level of hearing and here also, with considerable scatter In 20 cases, one or other form of tympanoplastic procedure was undertaken simultaneously with the operation Although the primary result was excellent in many cases, the permanent results here, as in other materials, were by and large, rather disappointing It is, however obvious that there was moderate displacement in the direction of improved hearing Isolated patients obtained good increase in hearing which appears to be permanent. Retention of hearing following radical operation must, per se, be considered to be a considerable achievement.

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INCIDENCE, ETIOLOGY AND PROGNOSIS OF ACUTE PURULENT OTITIS MEDIA IN HELSINKI RESIDENTS OF VARIOUS AGES

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5 180 cases of acute purulent otitis media were studied on basis of case histories and questionaires. Incidence for various age groups is illustrated. Etiology is studied on basis of other simultaneous infections and effect of hyperplasia of adenoids. Prognosis is judged by restoration of hearing, duration of discharge and complications

Introduction

It was the purpose of this paper to study the incidence of acute otitis media in different age groups and the etiology and prognosis of this disease. The survey is based on cases treated at the University Otolaryngological Hospital of Helsinki in 1961—1962. The material consists exclusively of patients whose ears, at the time of attending hospital, were found to be discharging or to contain pus after para centesis. Data on patients are derived from the history and from replies to question naires. While the total number of patients with otitis was 4069 the cases of acute otitis media (uni- or bilateral) totalled 5180 Thus relapsing otitis occurred in 1111 cases (21.5 %) The questionnaire was filled in and returned by 1085 patients (26.7 %)

Treatment consisted of paracentesis if the tympanic membrane was still unperforated when the patients presented themselves for treatment, and of aspiration of the middle ear Medical treatment was usually nose drops and penicillin, with the exception of some patients, especially those allergic to penicillin, who received sulfa or broadspectrum antibiotics.

Previous studies

Age distribution

Previous studies of the age distribution in acute otitis media have been reported as follows (Table 1)

The above studies, however show only the number of children of various ages treated for otitis media by physicians. They do not give the actual incidence of otitis in different age groups. This matter is more clearly illustrated by the series to be dealt with below based as they are on active observation of a definite population group and recording each case of middle-ear infection occurring during one year

In the study of Lowe and co-workers (1963) comprising 2039 children under 15 years, the incidence was found to be by far the highest in the age group below one year over 40 % of the children observed had otitis in their first year of life. For children of ten, the percentage was as low as approximately 3

TABLE 1

DISTRIBUTION OF ACUTE OTITIS MEDIA ACCORDING TO PREVIOUS STUDIES

The authors' name is followed by the year of publication and the total number of cases. In the studies marked with an asterisk the figures were represented graphically and slight errors are thus possible.

Age in years			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	>15
Rodger	1937	599	185	200	211													
Heller	1010	163	23	13	12	11	22	19	23	10	17							
Maxwell	1910	1514	352			306			283			572						
Hamberger	1942	371	71					28					17					255
Carlens	1943	1088	410										678					
Falbe-Hansson	1911	437	201		210								8					18
Grebelius	1949	329	22	35	24	30	23	23	11	13	13	12	16	5	6	2	2	83
Grebelius	1949	360	48	53	50	28	28	21	8	12	15	6	2	6	5	2	—	81
Lundgren	1949	210	73			141												
Bjuggren	1950	178	13	31	27	21	33	11	14	22								
Jerald	1950	266	30	187				56										13
Poulsen	1950	232	110	87	35													
Bjuggren	1952	131	10	11	21	21	19	20	16	7								
Heller	1953	1053	174	183	132	131	100	112	78	18	71							
Rudberg	1951	1356	81	137	229	157	148	138	281				203					
Sahoel	1958	210	122			88												
Fry	1958	552	108					213					113					
Stickler	1963	158	33	25	61				31				0					

The study undertaken by the Medical Research Council's Working Party (1957), however showed two peaks in the incidence one for children in their first year (13 7 %) and the other an even higher one for children of five (20.8 %)

Ebbs (1937) examined the ears of 880 children under 14 who had died of various pediatric and surgical diseases. He found that 52.8 had pus in one or both ears. Autopsy proved that otitis was most common in the group of children under one year (over 60 of all cases of otitis)

Miller and his co-workers (1960) observed 817 children throughout their first five years of life. Of these 163 (19.2 %) had an attack of acute otitis media during the observation period

Bowers material (1949) from New York included 793 cases of otitis. Approximately 45 % were children under ten.

Siirala made a study of the 6003 patients, treated in 1947—1951 at the Oto-laryngological Clinic University of Turku for ear diseases causing impairment of hearing He concluded that acute otitis media accounted for over 65 % of all ear diseases in children under ten. The corresponding percentage for those aged 80 years was 2.

Rate of bilateral and relapsing infections

Rodger (1937) found the attack rate of bilateral otitis for children in their first year to be 43.2 % for those aged 1—2 years 43 0 %, and 2—3 years 38.8 %.

Rudberg (1951) states that the rate of bilateral otitis in patients of 0—75 years of age was 21.5 %, whereas, according to Sohoel's study (1956) the percentage for children of 0—10 years was 30 0

In Ronning's study the rate of bilateral otitis was 61.8 % for the age group 0—5 45 % for the group 0—10 and 0 % for the 11—19-year old

Riskaer's (1945) figures are 70.8 % for the group 0—2 years 43.2 % for those aged 2—10 and 11 % for those over ten.

Miller (1960) claims that no less than every third child who has suffered from otitis media has at least one relapse before his fifth year

In the clinical material observed by Lundgren (1949) the relapse rate within six months was found to be about 15 % for children under three and about 3 % for children over three.

Fry's study gives a comparatively high relapse rate for the group 0—10 years, 40.3 %. For the group 10—20 his figure is 16.5 %.

In Poulsen's (1950) series, relapses occurred in 30 % of the children under three, distributed almost evenly among the various age classes.

The lowest percentage of otitis relapsing within one year in the age group under one year occurs in the report of the Medical Research Council's Working Party — 23 9 %. The maximum, 58.3 %, is found in the study of Lowe and co-workers (1963) The corresponding figure in Grebelius and Sjöberg's study (1949) is 41 7 %. According to the Medical Research Council's Working Party the relapse rate for children of 2—14 years is 21 0 % and for those aged over 15 years 4.5 %

The greatest decrease in the tendency to relapse has been reported by Grebelius and Sjöberg, according to whom it goes down to approximately one-half when moving from the 0—1 year age group to 1—2 years.

Present Study

Age distribution

The results of this study showed that otitis media occurred in the various age groups as follows (Fig 1):

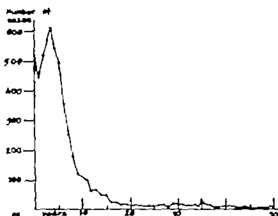


Fig. 1 Age distribution of cases in the present study

In order to illustrate the incidence of acute otitis media in different age groups, the author calculated the annual attack percentage for the residents of Helsinki on the basis of the number of cases treated at our Hospital and the average population of Helsinki in 1961—1962. It should be noted, however that a certain proportion of the ear infections occurring in Helsinki were treated by private practitioners or at the Municipal Ear Hospital. Thus, the figures here given may not be high enough for a fully reliable picture to be obtained of the incidence of otitis in people of varying ages. Yet the table would seem to give a reliable picture of the relations between the various age groups (Fig 2)

Figure 2 shows a steep and statistically highly significant drop in the frequency between the age of three years and slightly over ten when children are just past their liveliest growing period The curve then continues to decline slowly and relatively smoothly with increasing age. The oldest patient was 82 years of age From the above it can be concluded for instance, that the attack risk is approximately 15 times as great for the 3-year old as for youngsters of fifteen, and more than 100 times as great as for old people At first it may seem surprising that the rate of incidence also diminishes to some extent when moving from 3-year old to younger children This, however is only apparent and due largely to the fact that, because of the lack of autoanamnesis, otitis media in small children easily remains undiscovered

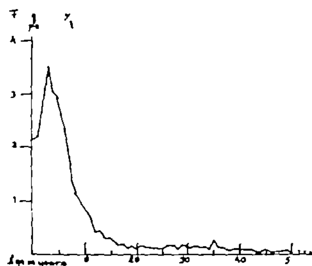


Fig. 2. Annual incidence of acute otitis media in Helsinki residents as calculated by cases treated at the university otolaryngological hospital of Helsinki, compared with the average population of Helsinki, in 1961—1962.

Rate of bilateral and relapsing infections

In the following, the author has studied the tendency to relapse in different age groups and the frequency of simultaneous infection in both ears. Both these factors give and idea of the susceptibility to otitis (Fig 3)

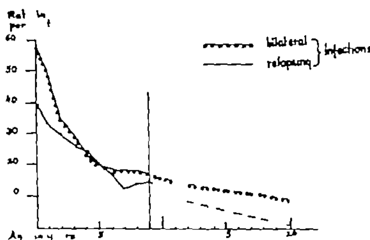


Fig. 3. Frequency of relapsing and bilateral infections in different age groups. (After the age of 8 the number of cases is small and so the results can only be appraised roughly.)

Figure 3 shows a statistically significant drop in the frequency of relapsing and bilateral otitis between the first year of life and the approximate beginning of school age, whereafter a further slow decrease is seen. Thus, if we estimate the susceptibility to otitis by the tendency to relapse and bilateral infections, a distinct conflict appears between figures 3 and 2: in the latter the frequency peak does

not fall on those under one year of age but on the three year old This seems further to substantiate the view that the reduced number of cases in the three youngest age groups in table 2 is actually due to diagnostic difficulties at that age.

Comparison between Previous Investigations and Present Study

This study like previous ones, shows that there is a steep drop in the incidence of otitis between play age and the termination of the period of most active growth. In this material, however the frequency peak falls not on those under one year but on the group of three years. This is completely in accord with most earlier studies listed in table 1 which indicate that the peak occurs in the group 2—3 years. In those studies, as in the present one, the patients first attended the hospital for treatment on their own or their parents initiative Studies based on active observation of a definite population group (Lowe et al., Ebbs, Medical Research Council) have given slightly dissimilar results. the peak tends to fall on the youngest age group, those below one year The Medical Research Council's curve as already stated, showed another even higher peak for the group of five years. A slight rise in the attack risk at this age also appears in the studies of Heller Lowe et al and Ebbs. The curve in the author s study does not indicate any such rise, although the curve is less steep for five-year old children.

According to the present investigation, the attack risk in the case of acute otitis media is approximately 15 times as great for children of three as for youngers of 15 In the study of Lowe et al. the coefficient is 6, and the Medical Research Council put it down as approximately 5. The incidence for children under ten is reported by Lowe et al. as about 15% and by the Medical Research Council s study as about 10 %. These figures are fairly high compared with the author s, which is only about 1.5 %. The author here wishes to re-emphasize the fact that all cases of otitis media in residents of Helsinki were not treated at the University Otolaryngological Hospital of Helsinki. Thus the figure is lower than the true incidence.

Approximately every second patient in the group below one year suffered from bilateral infections, which is in agreement with most of the reports previously published. The relapse rate for children in their first year in the present study is 39 6 % or roughly halfway between the lowest (Medical Research Council, 23.9 %) and highest (Lowe et al., 58.8 %) figures earlier reported. The tendency to relapse dropped to approximately one-half when moving from children under one year to the group 4—5 years, which agrees roughly with the findings of Lowe et al.

From all this it can be concluded that — in the light of the age distribution and the rate of bilateral and recurring infections — otitis media is mainly a childhood disease. The attack risk generally diminishes with increasing age although in some studies an occasional rise is found in children of approximately five years.

Etiology

Table 2 illustrates the diseases occurring either simultaneously with or before otitis. In most cases the etiology seems ovious. In cases in which otitis media was

accompanied or preceded by several of the diseases listed in table 2, it wa attempted as far as possible to discover the basic cause

TABLE 2

ETIOLOGY OF ACUTE OTITIS MEDIA

The group termed «n tiological disease» consists of cases in which the history or the replies t the questionnaire denied the presence of other simultaneous diseases

Distribution of cases			Distribution of cases		
Age < 1—15 years	Number	Percentage	Age over 15 years	Number	Percentage
Rhinitis ac	2990	90 9	Rhinitis ac.	292	6.2
Morbilli	97	2.9			
Sinuitis	36	1 1	Sinuitis	46	12.0
Tonsillitis ac.	27	0.8	Tonsillitis ac.	4	1 0
Varicella	12	0 4	Varicella	1	0.3
Pneumonia	6	0.2	Pneumonia	1	0.3
Pharyngitis ac	6	0.2	Pharyngitis ac	3	0.8
Parotitis epid.	5	0.2			
Scarlatina	2	0 1			
Lar ac.pseudocr	1				
Rubeola	1		Contusio auris	2	0 5
Corpus al. in meathus ac. ext	3	0 1	Corpus al. in meathus ac. ext	3	0.8
No etiological disease	103	3 1	No etiological disease	31	8 1
	3280	100 0		383	100.0

Table 2 does not include the 1506 cases in which it was not known whether or not any etiological disease was present As will be seen, 96.8 % of all patients under 15 had some other infection in addition to otitis. Whether and to what extent this other infection was actually an etiological factor is, of course, somewhat uncertain In 0 09 % of the patients otitis had obviously originated through the external auditory canal (traumatic rupture of tympanic membrane) In the age group over 15 years the figures are 90 6 % and 1.3 %

Inflamed and hyperplastic adenoids represent another causal factor in acute otitis media this group was considered in the light of the information given in the completed questionnaires. The results for the other patients are unreliable they may have suffered from a previous otitis treated elsewhere or may have had their adenoids removed in some other hospital.

Table 3 gives the proportion of patients (as per cent) with acute otitis media in 1961—1962 found to have enlarged and inflamed adenoids.

It should be noted that since, in the Outpatient Clinic in particular adenotomies are not readily performed on children aged under one year such children were also examined for adenoids less frequently than other age groups. Thus, their number as given in Table 3 is lower than in reality

It is seen that hyperplasia of the adenoids, roughly estimated occurred in every third otitis patient under ten.

The following table illustrated the effect of adenotomy on the attack rate of acute otitis media (Table 4)

TABLE 3

HYPERPLASI ADEN DS IN ARIOUS E GROUPS CHILDREN WITH OTITIS MEDI

Age, years	Incidence (per cent) of hyperplasia of adenoids	Age years	Incidence (per cent) of hyperplasia of adenoids
<1	26.6	6	34.1
1	24.2	7	36.0
2	33.0	8	32.1
3	40.8	9	37 1
4	36.1	10	30.0
5	32.6		

TABLE 4

EFFECT DENOTOMY O RELAPSE R TE OF CUTE OTITIS MEDI

Age years	Group 1	Group 2	Group 3	Total
1—4	80	13	36	129
5—15	70	7	46	123
T tal	150 (59.5 %)	20 (7,9 %)	82 (32,5 %)	252

Group 1 Adenoids removed, no relapses of otitis
Group 2. Adenoids removed, relapses may till occur but much more rarely
Group 3. Adenoids removed. R lapse rat unchanged

Table 4 is based on 252 otitis patients under 14 whose adenoids were removed in 1961—1962. In 150 cases (59.5 %), relapses of otitis ceased, at least for the time being, and in 20 cases (7 9 %) a definite decrease in the attack rate was evident. This would seem to prove that adenotomy was effective in 67 4 of the patients This figure, however must be viewed with a certain amount of reservation, since the observation period was quite short, in a few instances less than one year

The following table, based on data from the questionnaires, is designed to elu cidate the part played by adenoid hyperplasia in relapses of otitis media (Table 5)

Table 5 includes all children under 14 who replied to the inquiry It indicates that while adenoid hyperplasia was found in 22 % of the children with only one

TABLE 5

EFFECT OF HYPERPLASIA ENO DS N RELAPSE R TE OTITIS MEDI

		Pathologically enlarged adenoids (per cent)
Patients with only 1 otitis media		
) hyperplasia of adenoids in	80 cases	22
b) no hyperplasia of adenoids	292	
Patients with 1 relapse		
) hyperplasia of adenoids in	54	30
b) no hyperplasia of adenoids	125	
Patient with 2 relapses		
) hyperplasia f adenoids in	45	39
b) no hyperplasia of adenoids	70	
Patients with more than 2 relapses		
) hyperplasia of adenoids in	138	60
b) no hyperplasia of adenoids	91	

otitis, the corresponding percentage for children with a history of more than two relapses was 60 It may be remembered in this connection that as indicated by table 3 hyperplasia of adenoids occurred in approximately one third of all children with otitis. It should also be kept in mind, however that the adenoids were not examined in each case of acute otitis and that special attention was paid to them chiefly in cases with frequent relapses. Accordingly the differences between the groups in the table are certainly too large It must be pointed out in addition that the total of pathologically enlarged adenoids in table 4 does not agree with that in table 5 the former does not include the cases in which there was hyperplasia of the adenoids, which for some reason were not removed.

Prognosis

The prognosis has been evaluated by restoration of hearing, duration of discharge, and possible complications.

Restoration of hearing Table 6 illustrates the restoration of hearing after otitis media in those patients who attended the hospital for follow-up examination or returned the completed questionnaire in which the patient had

TABLE 6

RESTORATION OF HEARING AFTER ACUTE OTITIS MEDIA

Age Years	Hearing restored		Hearing impaired	
	No. of cases	Percentage	No. of cases	Percentage
3	38	97	1	3
4	41	100	—	—
5	55	98	1	2
6	40	95	2	5
7	26	100	—	—
8	21	100	—	—
9	14	88	2	12
10	9	100	—	—
11—20	38	100	—	—
21—50	15	88	2	12
over 50	3	100	—	—

Group A. Hearing tested by physician

Age Years	Hearing restored		Hearing impaired	
	No. of cases	Percentage	No. of cases	Percentage
3	83	92	7	8
4	69	96	3	4
5	65	93	5	7
6	43	88	6	12
7	36	95	2	5
8	26	93	2	7
9	16	84	3	16
10	13	93	1	
11—20	44	86	7	14
21—50	46	87	7	13
over 50	5	50	5	50

Group B Hearing appraised by parents etc.

been requested to describe his hearing before and after otitis. The following rating was used. hearing normal, slightly impaired, severely impaired, or deaf The patient was further requested to state whether his hearing had been tested by a physician or a layman. Only one case — appearing in table 9 — of subsequent deafness was found, this was caused by destruction of the labyrinth performed for purulent meningitis. Apart from this, the results were as shown in Table 6. It consists of two parts: the patients whose hearing was checked at the hospital or by a doctor elsewhere, and those whose hearing was appraised only for instance by the parents.

Table 6 based solely on hearing tests for speech and whisper (but no audiograms), represents only a rough analysis. Altogether 97 of the patients in group A tested by a physician, regained normal hearing In group B the figure is only 90 %. The percentage in group A is lower in each age group than in group B a fact which is statistically higly significant. This is probably due at least in part to the fact that the hearing in group A was restored at follow-up examination by certain procedures (e.g Politzer), thus indicating the importance of a follow-up Hearing was restored in 93 % of the cases included in table 6 and remained impaired in 7 %, in 0 4 % of these severely There were no distinct differences between age groups.

D u r a t i o n o f d i s c h a r g e. Data in the questionnaires indicated that in 125 cases — 2.4 % of all cases — the duration of discharge exceeded one week (Table 7)

TABLE 7

CASES WITH DURATION DISCHARGE EXCEEDING ONE WEEK

Duration of discharge 1 week t 1 month	105 cases	2 % of all
Duration of discharge over 1 month	20	0.4 %

The age groups were not found to differ significantly in regard to duration of discharge.

On the basis of 77 cases with known probably etiology selected from table 7 the basic diseases were found to be as follows (Table 8).

TABLE 8

ETIOLOGY ACUTE OTITIS MEDIA IN CASES WITH PATHOLOGICALLY LONG DURATION DISCHARGE

Rhinitis	Sinusitis	Hypertroph. tons. phar	Morbilli	Tons. acuta	N known cause	Total
46 cases 59 %	4 cases 5,2 %	13 cases 16.9 %	8 cases 10.4 %	2 cases 2.6 %	4 cases 5.2 %	77 cases 100 %

The part played by measles as an etiological factor represents 2.6 % of the total, but when only cases with long-standing discharge are considered, the difference is statistically significant.

C o m p l i c a t i o n s. Table 9 illustrates serious complications of acute otitis media in the series studied.

TABLE 9

SERIOUS COMPLICATIONS OF ACUTE OTITIS MEDIA

Complication	Age years	No of cases	Treatment
Mastoiditis acuta	<1—1	3	Mastoidectomia
Mastoiditis acuta	1—3	2	Medication
Mastoiditis acuta cum paresis nervi facialis	61	1	Mastoidectomia
Otitis interna serosa	57	1	Medication
Meningitis purulenta	70	1	Mastoidectomia. Nudatio durae matris cerebri. Trepanatio et canalisatio labyrinthi.
Abscessus cerebri	20	1	Mastoidectomia. Nudatio durae temporalis et sinus sigmoid. Punctiones absc. et remedia.

Paracentesis was performed on all patients

All the patients included in table 9 were discharged from the hospital convalescing

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EXTRATYMPANIC PHONOMETRY

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Contractions of th middle ear muscles cause eardrum movements giving rise to pressure changes in the closed ear canal. The registration of these (extratympanic manometry) is strongly impeded by the presence of noise (mainly pulse). By application of extensive noise reducing constructions and repetitive oscilloscope tracings a greatly improved sensitivity has been obtained.

In gro p of normal subjects a stapedius reflex has been recorded in both ears in all persons. The method is particularly suitable for latency determinations. The threshold of reflex by this procedure agrees with that obtained by the impedance method.

In some pathologic ears in which no reflex could be demonstrated by the impedance method the extratympanic phonometry has revelled the presence of a reflex.

Various procedures have been described for detection of the stapedius reflex in man

Direct inspection of the involved middle ear structures through a microscope.
Electromyography
Observation of changes in the acoustic impedance of the eardrum.
Extratympanic manometry i.e registration of pressure changes in the closed ear canal.

Of these methods only the two latter appear to be applicable in the clinic.

When the stapedius muscle contracts the ossicular chain as well as the eardrum will be displaced. The displacement may reach a state in which the eardrum plus the ossicular chain are characterised by different elastic properties being detectable for an impedance measuring device. However before this state — actually at the onset of volume displacement of the eardrum — a manometer may detect pressure changes in the ear canal. This method, the extratympanic manometry (ETM) may only reach a limited sensitivity due to the presence of noise generated by the pulse of blood vessels. The noise is mainly of very low frequencies. Hence we have applied a measuring system with greatly reduced sensitivity for low frequencies. The measuring instrument is, however not a manometer any more, it is a microphone with a specially shaped frequency characteristic and so we apply the term »extratympanic phonometry» (ETP) for this procedure.

The ear to be measured is connected through short and narrow tubing to a measuring microphone. After amplification and filtering the signal is finally displayed on an oscilloscope with a camera attached. The stimulus consists of 1000 Hz tone bursts applied to the contralateral ear The onset of the stimulus is used for triggering of the oscilloscope.

A substantial improvement of the signal-to-noise ratio has been achieved by repetitive reflex elicitations all recorded superimposed in one exposure on the photograph. Our investigations have all been carried out with series of 30 super imposed traces.

The trace of our microphone signal is not, like that of a manometer a simple graph of pressure in the measuring cavity It is drastically distorted due to the elimination of low frequencies. However the onset of a signal is correctly recorded both i regard to time of onset of the recording, and in regard to the sign of the initial deviation from the zero line

Although the initial direction of volume diplacement may thus be evidenced the direction of the corresponding malleus movement cannot be judged.

A displacement of a spherically shaped fibrous membrane produced by application of a pull at the center causes a volume displacement in the opposite direction. This example of the complex behaviour of membranes which are not flat shows that without an extremely detailed knowledge of the particular eardrum in question the direction of malleus displacement cannot be settled only from the inherent volume displacement of the drum.

Since the position of a membrane may be decisive for the magnitude and even the sign of its volume diplacements we have in all our investigations recorded the signal of an ear at three different pressures in the ear canal, usually —5 cm, 0 cm and +5 cm H_2O These three recordings will in general be of rather different shape and amplitude and have, in a number of cases, exhibited the above mentioned reversal of the initial deflection.

The set-up has a sensitivity sufficient to record volume displacements of the eardrum of 2 10^{-8} cm^3

ETP is an indirect measuring method just like ETM and the impedance method. Hence one cannot be completely sure that the stapedius muscle is the real cause of the observed reflex. Some observations which elucidate this question are men tioned below

The main reason for construction of the present apparatus has been the need for at better method for latency determination of the human acoustic stapedius reflex in the clinic.

By employment of the impedance method Metz (1951) reported latencies between 35 and 150 msec. In a similar way Møller (1958) measured latencies of 25—130 msec. These results are in complete agreement with our own experience using the same method. Holst et al. (1963) used ETM for latency determination. The latencies were all in the range 20—80 msec, the median value being 60 msec. EMG registration of the stapedius latency shows definitely shorter values. 10—18 msec (Perlman and Case, 1939 Fisch and Schulthess, 1963 Djupesland, 1965).

The difference between the latency time of EMG and that of the two indirect methods (ETM and impedance) relies upon mechanical delay mechanisms. ETP appears to be a method in which this mechanical delay is reduced considerably

The normal material comprises 28 normal hearing persons, i.e. 56 ears. A reflex has been detected in all ears. The shortest latency was 15 msec and the longest 42 msec. The median value in this material was 17 msec. In 32 years (57 %) a latency

of 15—17 msec was measured and only in one ear the latency exceeded 29 msec. The stimulus was in all cases 1000 Hz tone bursts at 100 db above hearing threshold.

Threshold determination of the acoustic stapedius reflex by ETP has been performed in some subjects. The results are in agreement with those obtained by the impedance method.

Also in other ways ETP has appeared to be useful. In some ears a considerable difference in magnitude of the reflex response obtained by the two methods (ETP and impedance) has been observed In six pathologic ears with normal ETP reflexes no reflex could be demonstrated by the impedance method. In two ears the reverse phenomenon was found However purely mechanical properties may account for these seemingly conflicting results The impedance method is sensitive only to changes in the elastic properties while ETP will detect nothing but fast volume displacements of the drum, and these different mechanical signals are not necessarily associated phenomena

A patient (male age 31) was investigated on the 6th day after the beginning of a Bell's palsy and repeatedly in the following weeks. He was tested by the impedance and ETP and the mobility of the facial muscles and the taste of the anterior 2/3 of the tongue were examined The lachrymal function remained normal. EPT showed decreasing reflex response in the first days of investigation. Ten days after the onset of the paresis no reflex could be demonstrated but from the 16th day an increasing reflex appeared By the impedance method we were not able to detect any reflex until the 20th day The variations of the ETP reflex were parallel with the changes in the taste and the mobility of the face.

A comparison of our ETP reflex recordings with EMG investigations of the acoustic tensor tympani reflex (Salomon and Starr 1963, Djupesland, 1965) shows that the latency by ETP is only 15—42 msec while the shortest latency by EMG is reported to be 80—90 msec. In addition EMG recordings show that a reflex of the tensor tympani in response to acoustic stimuli may be recorded exclusively in cases where a general startle reaction is observed. In our measurements only 1000 Hz at 100 db above the hearing threshold has been used as stimulus and we have not observed a startle reaction in any case. These findings indicate that the recorded ETP reflex is not a tensor reflex.

ETP may in our opinion be a valuable supplement to the impedance investigation in the study of the middle ear function As to latency determination in the clinic, ETP seems to be very suitable

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DETERMINATION OF THE AIRWAY RESISTANCE OF THE EUSTACHIAN TUBE

A NEW METHOD FOR ASSESSMENT OF THE EUSTACHIAN TUBE FUNCTION IN CASES WITH PERFORATED EAR DRUMS

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The method is based on principles employed in respiratory physiology. Measurements of the airway resistance of the Eustachian tube during different experimental conditions in ears with perforated drumheads will be reported.

Owing to a better operative technique and available antibiotics the possibilities to operate successfully on the middle ear have increased considerably over the last 15 years. Good results have also been reported from tympano- and myringoplastic surgery. Unfortunately there are also certain draw-backs. Some of these failures at operations may be due to reduced ventilatory capacity on the part of the Eustachian tube.

Methods for preoperative testing of the Eustachian tube function have been insufficient or lacking. In later years new methods for the preoperative study of this function have been reported. At Lund a method based on physiologic principles, the so-called aspiration method, has been worked out (Flisberg, Ingelstedt and Örtegren 1963).

Anatomically the Eustachian tube may be regarded as a part of the upper airway. Physiologically there are also certain similarities since ventilation of the middle ear takes place through the Eustachian tube. The methods and principles employed in respiratory physiology should thus also be applicable to the Eustachian tube.

In this way it would be possible to obtain an objective value of the resistance that originates at air passage through the Eustachian tube. Additional information about normal as well as pathologic physiology is to be expected.

Method

In respiratory physiologic studies of airway resistance the air flow ($\dot{V}$) through and the pressure difference (ΔP) across that part of the airway that is to be assessed are simultaneously measured (DuBois 1962, Comroe 1961). The resistance (R) can then be calculated according to the formula

$$R = \frac{\Delta P}{\dot{V}}$$

For determination of the air flow resistance in the Eustachian tube according to these principles the air flow through and the pressure difference across the Eustachian tube must be measured.

An air flow through the Eustachian tube is obtained if there exists a pressure difference between its two ends at the tubal opening, e.g. at deglutition. In the present investigation such a pressure difference was produced by application of over or underpressure in the nose or ear.

Simultaneous pressure measurements in the nose and ear made it possible to determine the pressure difference exactly.

The air flow was measured by a flow meter device which could be airtightly connected to the external ear canal. At air passage through the Eustachian tube the air also passed through the flow meter device on condition that there was a perforation of the ear drum.

Equipment

The flow meter consisted of a resistor which on both sides was connected to a differential pressure transducer by side tubes. Four different resistors could be used separately in the flow meter device. The resistors were: a Fleisch pneumotachograph (nr 2040) and three resistors devised by the author each consisting of five glass capillaries coupled parallel. The capillaries in one resistor were of the same kind but the calibres and lengths varied from one resistor to another. The differential pressure transducer (pneumomanometer EMT 572, Elema Schönander AB Stockholm, Sweden) had a pressure range of ±50 mm water. By using different resistors in the flow meter device the measuring range could be varied between 0 and 14 ml/sec.

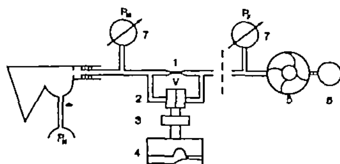


Fig. 1. Principle of air flow resistance measurements

1 Resistor in the flow meter device
2 Differential pressure transducer
3 Amplifier
4 Recorder
5 Electric fan
6 Autotransformer
7 Manometer

P_F = pressure generated by an electric fan
P_M = pressure in the middle ear
P_N = pressure in the nose

The flow meter device was connected airtightly to the middle ear by a nylon catheter (inner diameter 2 mm) which passed through an inflatable rubber cuff lodged in the bony part of the external ear canal (fig 1) The other side of the flow meter device was open on to the atmosphere or could be connected to a pressure producing apparatus (an electric fan)

In the amplifier of the differential pressure transducer the air flow signals could be integrated so that an expression of the air volumes passing the Eustachian tube was obtained.

In the nose, over or underpressures could be applied by the method devised by Ingelstedt and Örtegren (1963) The same equipment was used to create over or underpressures in the ear The pressure producing apparatus was then connected to that part of the flow meter device which faced the atmosphere.

To record the pressures in the nose and ear two pressure transducers (EMT 400 A and B Elema-Schönander AB Stockholm Sweden) with pressure ranges, respectively 0—300 mg Hg and 0—30 mm Hg were used. The transducers were connected to the nose and ear equipments by short nylon catheters.

As recording instrument a Visicorder (model 906 S Honeywell) was used. All recordings could be made simultaneously

Calibration

The flow meter device was calibrated with known constant air flows and with known air volumes. Fixed calibration curves were obtained in this way for every resistor used in the flow meter device.

The pressure transducers were calibrated with ordinary water manometers. Frequency response analysis of the recording systems was made in model experiments. The frequency response was found to be sufficient for the investigations performed.

Material

The material consisted of 46 cases. Forty-one of these had chronic otitis media with a dry central perforation of the ear drum. In addition to the chronic otitis media, two cases also had a verified patulous tube (tuba aperta). Five cases had normal ear drums but symptoms of patent tube In these cases incisions of the ear drums were performed. These incisions were 3—4 mm long

The ears were divided according to their Eustachian tube function One group consisted of ears with patulous tube (7 cases) one group (20 cases) could equilibrate underpressures applied in the middle ear and one group (19 cases) lacked equilibration capacity In the last group passage through the Eustachian tube could be obtained by application of overpressure in the nose at deglutition

Results

Examples of different testings are given in fig 2 and 3

In fig 2 a patient with chronic otitis media and a good Eustachian tube function was examined at application of graded overpressure in the nose during degluti-

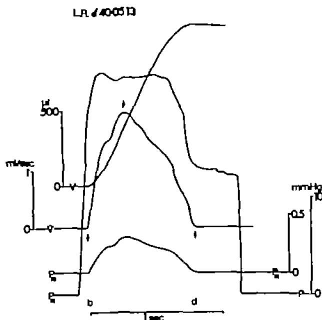


Fig. 2. Combined pressure and air flow measuring in case of chronic otitis media tested with graded inflation t pressure difference of 30 cm H_2O over the Eustachian tube.

) pressure pplication in the nose
b) opening f th Eustachian tube
) point of maximal air flow
d) closure of the Eustachian tube
) ending f pressure application
f) beginning of level air flow

V = volume of air passing the Eustachian tube
V = air flow thro gh the Eustachian tube
P_M = pressure in the middl ear
P_N = pressure in the nose

(The arrows correspond t the different letters)

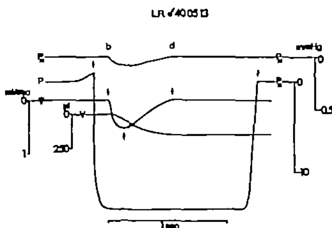


Fig. 3. Combined pressure and air flow measuring by application of underpressure in the nose in case of chronic otitis media. The pressure difference over the Eustachian tube was 20 cm H_2O (for symbols see fig. 2).

tion The Eustachian tube function had been assessed from the capacity for equilibrating an applied underpressure in the middle ear The minimal air flow resistance, i.e. the resistance at the maximal air flow through the Eustachian tube (at point c), was calculated at a pressure difference of 30 cm H_2O across the Eustachian tube The resistance was 15 cm H_2O/ml/sec

If in the same case an underpressure was applied in the nose, curves according to fig 3 were obtained The minimal air flow resistance at a pressure difference of 20 cm H_2O across the Eustachian tube was 37 cm H_2O/ml/sec.

At various pressure differences across the Eustachian tube the minimal air flow resistances were determined and a pressure-resistance diagram for one case with chronic otitis media and one patulous tube case was sketched (fig 4) In the case with chronic otitis media the air flow resistance was reduced at increasing pressure differences by applying overpressures in the nose. By application of underpressures in the ear whereby air was aspirated to the ear at the tubal opening and normal physiologic conditions were reproduced, increasing air flow resistances were obtained at increasing pressure differences.

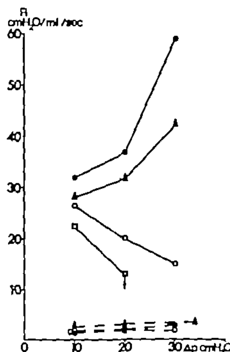


Fig. 4 Air flow resistances at application of various pressure differences over the Eustachian tube in a case of chronic otitis media and patulous tube case.

●—● Underpressure applied in the nose
○—○ Overpressure applied in the nose (graded inflation)
▲—▲ Underpressure applied in the ear (aspiration)
□—□ Overpressure applied in the ear (deflation) (arrow indicates spontaneous emptying)
Continuous line — chronic otitis media (L.R. 400813 ♂)
Interrupted lines — patulous tube (E.A. 081037 ♂).

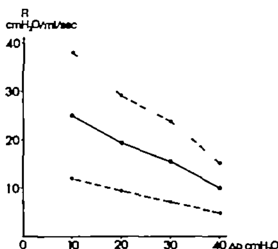


Fig. 5. Mean minimal air flow resistances and standard deviations of ears with good Eustachian tube function tested by graded inflation.

O—O mean air flow resistance
— mean air flow resistance ±1× standard deviation.

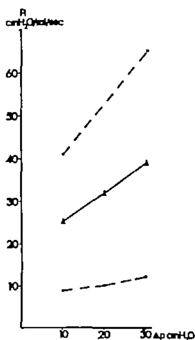


Fig. 6. Mean minimal air flow resistances and standard deviations of ears with good Eustachian tube function tested by aspiration method.

▲—▲ mean air flow resistance
— mean air flow resistance ±1× standard deviation.

In the patulous tube case very small differences in the air flow resistance could be seen at various pressure differences.

Great differences in resistance values were seen on comparison between inflation and aspiration testings. This is exemplified in fig 5 and 6 where pressure resistance diagrams were sketched after testing a series of ears with good Eustachian tube function. It is seen how the resistances were reduced at inflation testing but at aspiration the resistances increased at increasing pressure differences across the Eustachian tube.

For a comparison of ears with different Eustachian tube function the air flow resistances were determined at inflation testing with graded overpressure in the nose during deglutition. (Table I) Ears with patulous tubes had low air flow resistances (< 5—6 cm H_2O/ml/sec.) In ears with a good Eustachian tube function the air flow resistances ranged between 5 and 50 cm H_2O/ml/sec. In cases where passage through the Eustachian tube only could be reached with high inflation pressures (>20 cm H_2O) the air flow resistances were above 50 cm H_2O/ml/sec.

At sufficiently high overpressures in the nose the Eustachian tube could be kept open even after completed deglutition as long as the overpressure remained. This was recorded as a level in the air flow curve (fig 7).

TABLE 1

AIR FLOW RESISTANCES OBTAINED AT GRADED INFLATION TEST NO. I IN EARS WITH DIFFERENT FORMS OF EUSTACHIAN TUBE FUNCTION

	Number of ears	Air flow resistance (R) in cm H_2O/ml/sec
Patulous tube	7	<5— 6
Chronic otitis media — good Eustachian tube function	20	5— 50
Chronic otitis media — bad Eustachian tube function	19	50—200

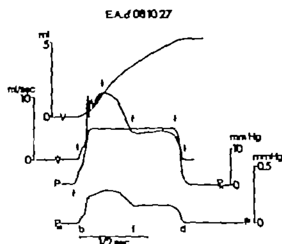


Fig 7 Recordings from a patulous tube case at testing with graded inflation at a pressure difference of 20 cm H_2O over the Eustachian tube (for symbols see fig. 2).

Discussion

A normal middle ear function requires a normal ventilatory function on the part of the Eustachian tube. That implies that pressure equilibrium is maintained between the middle ear and the atmosphere, i.e. the same pressure exists on both sides of the ear drum. If pressure equilibration is difficult owing to increased resistance in the Eustachian tube, an underpressure arises in the middle ear. The reason for this is a gas diffusion from the closed air space of the ear. This under pressure, which according to van Dishoeck (1941) can reach values of —50——60 cm H_2O may result in complications such as transudation (e vacuo theory according to Bezold 1883) and hearing impairment.

The present method makes it possible objectively to assess the ventilatory capacity of the Eustachian tube by measuring the resistance to air flow.

In ears with a poorly functioning Eustachian tube the air flow resistance values were high, while ears with patulous tubes had very low resistances. An intermediary group was made up of ears with a good Eustachian tube function.

The reason for these differences in resistance seems to be a change in the mechanism regulating the opening and closing of the Eustachian tube. The opening is produced by contraction of the tensor veli palatini muscle (Rich 1920, Graves and Edwards 1944). The closing of the Eustachian tube takes place passively and is due above all to the spring effect of the tubal cartilage but also to tissue pressure and muscle tonus (Perlman 1939, Zöllner 1942).

The reason for the patulous tube state is probably reduced capacity for closing the Eustachian tube because of changes in the mucous membranes or the surrounding tissues. Trophic mucous membrane changes after trigeminal neurectomy may be one reason (Handl 1959), reduction of the fat surrounding the lumen of the Eustachian tube (Ostmann 1893) another.

In chronic otitis media, mucous membrane changes may have originated in the middle ear and probably also in the Eustachian tube. Mucous membrane thickening and adherences may then interfere with the opening of the Eustachian tube. Serious infections may also lead to more far-reaching tissue changes and strictures and stenosis of the Eustachian tube may appear. Such changes naturally affect the air flow resistance at air passage through the Eustachian tube.

A pressure from the nose or ear affects the elastic walls of the Eustachian tube during the opening phase. An overpressure in the nose or ear dilates a normally functioning Eustachian tube. This implies a reduction of the air flow resistance at increasing pressure differences across the Eustachian tube. An underpressure on the other hand gives increasing resistances at higher pressure differences, indicating a tendency to suck the walls close. In poorly functioning Eustachian tubes the tendency towards dilatation is considerably less and is obtained only at high pressure differences. In these cases this indicates a stiffness of the tubal walls possibly due to some form of stricture or stenosis.

Owing to its dilating effect an overpressure may cause a constant air flow through the Eustachian tube after completed deglutition. During this air flow the pressure from the outside is balanced by the pressure from the tissues. In ears with poorly

functioning Eustachian tubes a high pressure was necessary to give a constant flow of air The counter-pressure from the tissues was high — probably owing to tubal stenosis. In ears with patulous tubes the required pressures were low

With the present method it is possible to study the Eustachian tube function in a way that has not earlier been feasible Objective information on the resistance to air flow through the Eustachian tube as well as on normal and patho-physiologic condition may be obtained

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PROTEINS OF MIDDLE EAR SECRETION IN SEROUS OTITIS

AN ELECTROPHORETIC AND IMMUNOELECTROPHORETIC STUDY

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From th Hospital Otolaryngological and from the Children s Hospital, University f Helsinki

The protein fractions of the middle ear secretions of 22 patients with true serous titis were tudied electrophoretically and immunoelectrophoretically The total protein of the secretion varied from 0 4 to 10.5 g/100 cc, mean 4.5 g/100 cc. The lectrophoretic protein pattern of the secretion was mostly similar t that of the serum. The relative albumin content seemed t be little lower and that f gamma globulin little higher than in serum. A ery small amount or no γM immunoglob lin was present in the secretion, while γA was clearly demonstrable in little more than half of the cases.

Secretory or serous otitis was described by Politzer (1908). In spite of innumerable and comprehensive studies on this disease the etiology and pathogenesis is still obscure (Bateman 1957 Carlson and Lbkk, 1955· Hopp et al. 1964 Siirala,1964 Suechs, 1952). It is not known whether serous otitis and adhesive otitis are different diseases or whether the latter is the late form of an untreated serous otitis, as has been suggested by Siirala (1964).

In thi study observations were made on the protein fractions of middle ear secretion in serous otitis. The following criteria were used for the diagnosis: 1 The hearing of the patient has become more or less impaired without any subjective or objective signs of infectious otitis media. 2. The tympanic membrane is indrawn and atrophic. 3. The Eustachian tube is closed. 4 When punctured, sterile clear yellowish, serous or viscous secretion is obtained from the middle ear 5 When the tympanic cavity is aerated the hearing of the patient improves, at least temporarily

Material and methods

One or more samples from the middle ear fluids of 22 patients with serous otitis were studied. The ages of the patients varied from one to 84 years, mean 22 years. Ten of the patients were females and 12 males. The samples were obtained either by punction through the tympanic membrane or fluid from the antrum was aspirated in connection with surgical operations.

All the patients suffered from chronic serous otitis. Either adenotomy or combined adenotomy and tonsillectomy were performed on 15 of the 22 patients. None of the patients showed allergic signs. During the time of sampling paranasal sinuitis was not present in any of the cases. Serous otitis was bilateral in 14 cases. The samples from the middle ear fluids and aliquots of the sera of the same patients were stored at —20°C until they were analysed.

The tot l protein content of th samples was estimated by th biuret reaction. Paper electrophoresis of the middle ea secretions a d the sera of the same patients was carried out at pH 8 6. The run was made at constant voltage of 110 V for eight hours. After staining the trips w th amido black th relativ content f different protein fractions were estimated with a Zeiss densitom t r

The immunoelectrophoresis was carried out according t th micromethod of Scheidegger (1955). Horse anti-human serum from the Pasteur Institute (Lot number 223) was used for the precipit tion of the fractions.

The possible presence of gamma A immun globulin (γA IgA) in the middle ear secretions was also tudied b microdiffusion in agar using a specific anti-γA serum (Behringwerk) for the precipitation (Crowle 1958).

Results

The total protein content of the middle ear fluid varied from 0 4 to 10.5 g/100 cc mean 4.5 g/100 cc. The lowest value was observed in the secretion of a patient th serous otitis of whom had been treated with several punctures before taking the sample for the present study The repeated punctures seem to cause at least in individual cases a decrease in the total protein content of the secretion. (Table 1).

TABLE 1

OTAL PROTI IN CONTENT IN CONSECUTIVE SAMPLES OF TI E MIDDLE EAR FLUID OF A 9- E R OLD GIRL UFFERING FROM T UE SEROUS TITIS

Dat	T tal protein of th middle ear fluid
January 25, 1962	9 0 g/100 cc
February 13 1962	3.6 g/100 cc
March 21 1962	1 7 g/100 cc
April 3, 1962	1 6 g/100 cc
May 11 1962	3 0 g/100 cc

\ the last sample was taken the patient showed signs of acute nasopharyngeal infection

As can be seen from Table 2, the electrophoretic protein pattern of middle ear secretion resembles closely that of the serum. The relative concentration of gamma globulin seems to be higher in the middle ear fluid than in the serum, while the albumin content is a little lower in the secretion The mean absolute concentration of gamma globulin however is at the same level in the secretion and the serum

TABLE 2

ELECTR PH RETIC PROTEIN FRACTIONS O THE MIDDLE EA SECRETI S AND ERA OF 21 TIENTS WITH TRUE SEROUS OTITIS

	Percentage of electrophoreti protein fractions					T tal protein g/100 cc
	lbumin	alfa 1 glob lin	alfa 2 globulin	beta globulin	gamma globulin	
Middle ear fluid	56.8 (34 9—71 2)	1 4 (1 9—8.8)	8.8 (1 9—14.3)	10 7 (3 7—21 8)	21.3 (7 1—35.6)	4 6 (0.4—10.5) 10 samples
Serum	62.0 (52.3—77 0)	3.9 (1.2—5 9)	8.6 (5.5—13 0)	11 6 (7 7—20.8)	13.2 (6.9—21 4)	.3 (5.6—8.3)

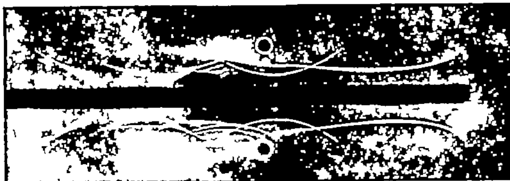


Fig. 1 a.

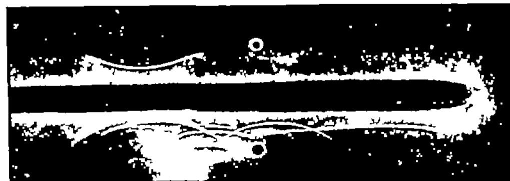


Fig. 1 b

Fig. 1 Examples f immunoelectrophoretic protein patt rns of middle ear fluids in serous otitis. On each slide the pper immunoelectrophoresis is that f the secretion nd the lower one is carried out from the serum.) The fractions of middle ear fluid and serum are nearly identical. b) Only albumin and traces of fou ther fractions were seen in the middle ear flu d in this case

In immunoelectrophoresis (12 samples) with an antiserum against the whole pool of human serum proteins the middle ear fluids showed 5—11 bands (Fig 1). In most cases the immunoelectrophoretic protein patterns of the secretions and the corresponding sera were surprisingly similar in several respects. The bands of γ C transferrin and albumin were seen regularly In addition, 1—2 fractions in the α1-area, 2—5 α2 fractions, and 1—2 bands in the β-area were seen In two of the 12 secretions studied immunoelectrophoretically a very faint band of γM was seen, while in the remaining cases this fraction was lacking. In microdiffusion in agar with a specific antiserum against the γA immunoglobulin this fraction was found from the middle ear secretion in eight of the 15 samples available for this study

Discussion

This study gives further evidence for earlier observations that the protein pat tern of the middle ear fluid in serous otitis greatly resembles that of the serum (Carlson and Lökk 1955 Hopp et al., 1964, Suechs, 1952) It has been reported that the gamma globulin level is higher in the middle ear fluid than in the serum

(Carlson and Lökk, 1955) In this study too the relative concentrations of gamma globulin in the secretion exceeded the serum levels (Table 2) The mean absolute concentrations, however were practically identical. Compared with serum, the middle ear fluid seems to be deficient in γM immunoglobulin content. This is in accord with the general physiologic appearance of this protein Because γM is a macromolecular protein (Mw about 1 million), its access to the interstitial fluid and secretions is limited (Gitlin 1966) If there were a local synthesis of γG immunoglobulin in the middle ear as has been suggested (Carlson and Lökk, 1955), there probably should be also a more regular presence of the γM. Antigenic stimulus causes primarily formation of γM antibodies, which is then followed by γG antibodies (Gitlin, 1966 Smith et al., 1964).

It seems very probable that the proteins of middle ear fluid derive from the serum The varying protein concentrations may be explained by the absorption of water from the secretion.

An immunoglobulin very similar to γA is known to occur in various secretions of the body (Gitlin, 1966 Keimowitz, 1964 Remington et al. 1964 South et al., 1966 Tomasi et al., 1965) In nasal and bronchial secretions an immunoglobulin of the γA type is the predominant protein fraction (Keimowitz, 1964 Remington et al 1964) In spite of the similarities between the serum and secretion γA, they are not identical (Tomasi et al., 1965) At least in the salivary glands there seems to be a transport of γA from the serum into the secretion It has been suggested that in the course of this transport a protein called »transport piece» is bound with γA, resulting in a change in the antigenicity and increase in size of the γA molecule (South et al, 1966) Though γA was clearly demonstrable in middle ear fluid of serous otitis in more than half of the cases, it cannot be said to form a predominant fraction in this secretion The varying content of water in middle ear secretion of this disease may however mask the true level of γA present under normal conditions.

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DISCUSSION

T. Palva, Oulu, Finland, to Aro

In this talk Dr. Aro mentioned that metaplastic changes are associated with different amounts of fluid in secretory otitis media. It should be made clear that metaplasia as such is not associated with the presence of secretion. The middle ear mucosa normally is of cylinder-cell type; poor Eustachian tube function and presence of fluid causes marked edema in the mucosa and in the number of goblet cells and of secreting glands but not necessarily any squamous metaplasia. Together with filtration from the capillaries, the secretory elements are responsible for the vicious cycle seen in secretory otitis.

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EFFECT OF CERTAIN EYE OPERATIONS ON THE ELECTRONYSTAGMOGRAM

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Electronystagmography was performed on 40 patients with one eye enucleated and on 20 patients who had undergone corrective surgery of the ocular muscles for strabismus. A part of the material had to be eliminated because the purpose was to study patients with healthy vestibular function whose possible ENG changes are due solely to ocular changes.

No significant change was seen in the ENG of patients with one eye enucleated. Small transfers of individual rectus muscles do not affect the ENG curve, but muscle resections and more complicated muscle operations have a suppressing effect on nystagmus or, in other words, a lowering effect on the amplitude of the ENG curve. This influence does not extend in the same ratio to the maximal intensity because calibration changes.

The purpose of the present investigation was to discover the possible sources of error in an indirect measuring method such as electronystagmography. The function of the vestibular organ is studied in fact by means of eye movements.

The question at issue was the changes that may occur in the ENG if vestibular function is normal but the function of the indicator, i.e. the eyes, is disturbed. How much does the ocular function change if one bulb is removed, and is it possible to modulate the values obtained to normal values? How does the ENG curve change if the oculomotor muscles have been operated on in connection with strabismus, producing limitations of movements?

We received excellent help from the Eye Hospital, University of Helsinki, which made available to us patients for whom enucleation was planned or who were to be or had already been operated on for strabismus. There were unfortunately only four patients on whom we were able to perform ENG both before and after the enucleation of one eye, but we compared the curves for patients enucleated earlier with the normal curves for the corresponding age group at our clinic. We obtained both pre- and postoperative curves for the patients operated on for strabismus.

I) Enucleated cases.

The ENG study was performed on 40 patients of whom 36 had been operated on before the measurement. Four patients were examined both pre- and postoperatively.

The indication for the enucleation of one eye was mostly either direct local trauma or glaucoma in one eye. The age of the patients ranged from 10 to 56 years.

The investigation was performed with a 1-channel ECG apparatus (Mingograf) furnished with a preamplifier and the electrodes were fixed to the lateral edge of the orbit. The inclination of the patient's head from the horizontal plane was 30 deg. and calibration 10 deg. Calorisation of both ears was done for 30 sec. with

water of 30°C. A detailed history was taken and pure tone audiograms were recorded for all the patients.

As the intention was to collect expressly material of normal vestibular function, we had to eliminate patients with skull trauma who had lowered vestibular function and also some cases with a history of vertigo and disturbed vestibular function The final material thus comprised 22 patients with unimpaired vestibular function and one eye

II) Patients with strabismus:

ENG was done both pre- and postoperatively on 20 patients undergoing corrective surgery on the ocular muscles for strabismus. The pre-operative study was performed 24 hours before surgery and the postoperative at the earliest 1 month, an average of 6 weeks, after surgery A pure tone audiogram and detailed history were taken from all the patients.

To obtain an accurate idea of the reactions of operated and non-operated eyes a study was performed with an ECG apparatus (Mingograf) furnished with a 2-channel preamplifier The electrodes were now attached temporally and nasally separately for each eye Calorisation of both ears was done with water of 30°C and the experimental conditions were otherwise also the same as above.

Results of the Investigation

Enucleated — As we had been unable to find in the literature any report on the effects of enucleation of the eye on the electronystagmogram, we assumed that the amplitude may perhaps diminish to a half its value.

We were unable to show that enucleation of one eye produced any significant changes in the electronystagmogram. Operation did not seem to have any appreciable influence on the amplitude or the duration.

Strabismus operation — We had intended to calculate the maximum intensity separately for each eye of the patients with strabismus. But it appeared, as was indeed natural, that the calibration curve changed in ratio to the actual ENG and thus the plan was abandoned The values kept constantly within the 13.7—16.5 /sec. range

The commonest operation was retroposition of either the temporal or nasal rectus muscle. No differences were established after these operations. This is natural in view of the mildness of the trauma when the muscle is separated from its insertion and is transferred a few millimetres. There were ten such cases, a half of the total.

After resection of the rectus muscles, there was a diminution of 2—3 mm in the amplitude but the maximal intensity did not change, as again was only natural. These cases totalled six

Corrective operations were performed on both eyes of the remaining four patients during the same hospital stay No difference was recordable in these cases.

The results warrant the conclusion that enucleation of one eye is no contraindication for ENG If a pathologic ENG curve is obtained in such a case, the reason must be sought either in the vestibular organ or more centrally

In the same way as fixation with the eyes open has a moderating effect on nystagmus, certain eye operations have this influence when the eyes are closed. This should be remembered in clinical work. If a successful operation has been performed on a squinting patient he does not like to report it to the physician examining his ears, as we have noted in practice.

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DISCUSSION

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The study of the one sided enucleated cases is really interesting. The results are a good support for the concept of the mechanism behind electronystagmography.

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A SIMPLE OPERATION FOR PROMINENT EARS

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A simple method is described for correction of prominent ears utilizing the spontaneous bending tendency of the auricular cartilage following scratching of its anterior surface. The scratching brings about desirable sharpening of the antihelix and posterior crus fold in the common type of prominent ears and in addition to this eliminates an undesirable folding in the lop ears.

A good many ear deformities have one feature in common namely that the ears are prominent. Apart from prominent ears in the usual sense of that term, there are also lop-ears, shell-ears, satyr ears and invaginated ears, for example.

With lop-ears, the upper posterior part of the ear hangs more or less forward towards the crus helicis, so that the ear can be as it were folded double. It is a normal condition during the third foetal month but towards the end of that month, the ears generally begin to straighten out again. Lop-ears are sometimes referred to as cup-ears, cat-ears and microtia. The latter term is applied to the ears as they appear to be so small. However when a microtic ear is straightened out, there proves to be hardly any or no difference in size between it and a normal ear on the other side.

Shell-ears can be described as prominent ears with more or less incomplete curling of the helix edge, and absense of the antihelix and crura so that the concha and scapha go directly over into one another.

Satyr ears are characterized by a pointed outline in the upper part with incomplete curling of the helix edge at the same point and deformation of the posterior crus. This is roughly what the ears look like for the greater part of the foetal development until the last months. It is only during the eight foetal month that the helix edge begins to curl over. The satyr tip corresponds to the anterior corner of the upper part of an animal's ear whilst Darwin's tubercle corresponds to the actual tip of an animal's ear. In humans, therefore, Darwin's tubercle lies behind and below any possible satyr tip.

Invaginated ears are a deformity in which the upper part of the ear is more or less embedded under the skin at the side of the skull. Other names are pocket ears and kryptotia. The deformity involves not only a cosmetic condition but also brings about functional difficulties. These patients are prevented by natural causes from wearing spectacles. The cause of the deformity has been taken to be, among other things, a congenital defect of the scapha part of the ear.

The operational procedure I shall come on to describe can be used for all the above-named deformities in so far as it is a question of correcting the prominent position. In order to correct the particular deformity special extra measures are needed for every one. Apart from the treatment of prominent ears in the usual meaning of the term however I shall only describe en passant a procedure for the correction of lop-ears.

But first some details about normal ears and prominent ears of the common type For a normal ear the angle between the plane of the ear and the median plane is about 30 but behind the ear there are actually two angles to take into account — one between the skull side and the concha and another between the concha and the scapha The former is broadly speaking the same for both normal and protruding ears i.e about 90 The latter varies considerably In normal ears, it is between 90 and 120 In prominent ears the angle is enlarged beoynd this figure Measured in cm 2 cm is reckoned to be the upper limit for a normal distance between the upper helix edge and the skull side for fully-grown ears.

When then are the ears fully grown? It used to be thought that ears had finished growing after 7 or 8 years. However more recent research has shown that the width of the ears and their distance from the skull side changes very little after the 10th year whilst the length continues to grow gradually into adult years. As early as the 3rd year the ears have been found to attain 85 % of their full development. On average, a fully grown ear is said to be 6.5 cm long and 3.5 cm wide.

As far as the size of the ear is concerned it may be worth pointing out that it is largely the relation between the ears and the size of the skull which decides whether or not an ear should be regarded as prominent. A small ear may seem quite normal even if the scaphoconchal angle is large. In children with comparatively large ears in relation to their skull it often seems as if the ears protrude rather a lot but as the skull grows, the deformity may well become less noticeable or disappear altogether

When is a good time to operate on children for prominent ears? In fact there ought not to be anything to prevent an operation at any age at all but most specialists agree that a good time to operate on children is before they start school and are made fun of by their fellows. Most of our patients are aged 5—6 and even then the operation can virtually always be performed with a local anaesthetic without encountering protests from the small patients. Our treatment is entirely policlinical.

Review of some methods of correcting prominent ears

In 1845 Dieffenbach suggested the excision of a wedge of skin from the posterior side of the ear Needless to say the favourable effect was of short duration, the ear gradually returned to its original position because of the elasticity of the auricular cartilage. It therefore became usual among Dieffenbach s successors to make an additional cartilage excision. However this excision was made where the auricular cartilage joined up with the side of the skull so that the effect was to reduce the cephalo-conchal angle. As was stated above, this angle is the same for both normal and prominent ears, and so the cosmetic result was unsatisfactory the whole of the ear became set too close to the skull side. In 1010 Luckett became the first to realise that an important reason for the prominence of an ear lies in the fact that the scapho-conchal angle is too great In other words the antihelix fold is not sufficiently marked. Luckett therefore made his cartilage excision where the concha goes over into the scapha, thus making the antihelix ridge stand

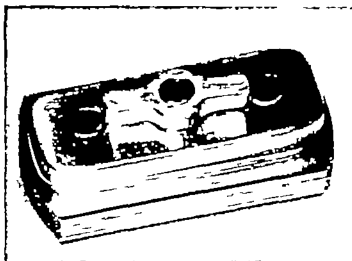


Figure 1 The original scratching instrument consisting of 15—20 razor blades in holder

out to the required extent Many successors have varied his procedure in various ways. A common feature of Luckett s method and most of its variations, however is that the antihelix and posterior crus are generally characterized by disturbingly sharp and irregular edges.

In 1947 Pierce et al. described how to make a rounded antihelix ridge. Eight to ten parallel cartilage incisions were made along the posterior side of the projected fold, whereby care had to be taken not to cut right through to the anterior cartilage surface.

The present author tried the Pierce procedure, but found it difficult to prevent the knife cutting right through the cartilage over and over again and so producing an angular outline again on the anterior side of the ear However by replacing the knife by an instrument consisting of 15—20 razor blades packed together in a holder complete severing of the cartilage could be avoided and good results obtained (Fig 1). Scratching was done by the corners of the packed razor blades, which formed a cutting edge of about 3 mm. The resistance of the auricular cartilage could be reduced sufficiently within a few seconds.

However in 1961 the present writer amended his procedure in an important respect In order to find out how deep the scratching went into the cartilage he had scratched plane sections of ear cartilage from a corpse Since the cartilage sections immediately curled over strongly and uniformly it was natural to think that this change in shape could be exploited for the correction of prominent ears (Fig 2). Since the cartilage curled away from the scratched surface, it was necessary to attack the anterior side of the auricular cartilage and a new scratching instrument was requisite in order to avoid unnecessary exposure of the cartilage surface

The writer s present procedure for correction of prominent ears

After due cleansing of the ears, we fasten strips of Scotch tape above and behind the ears if the patient happens to have long hair otherwise the hair has a disturbing

Fig re 2 Sections f l er uricular cartilage taken from ymmetric areas. A. Intact cartil-ge B One side f th rtilage scratched f llowed by a spontaneous folding towards it opposit side. 30 ×



Figure 3. Patient draped by rolling length of tockinett over the head and neck.

tendency to tumble into the operation area. We then draw a length of stockinnette over the patient's head (Fig. 3). We keep the stockinette in sterilized packs, cut to suitable lengths and rolled up to form a ring with a knot at one end. When the stockinette has been rolled on, a cut is made as far as the neck on each side whereupon the adjacent corners are knotted together. The ears are pulled out through very small slits in the stockinette.

The first thing to do now is to mark in dye where the antihelix fold and the anterior and posterior crus should run. These anatomical details can be seen easily if the ear is bent back towards the side of the skull (Fig. 4). If the posterior conchal wall is high, it transpires that the correct place for the antihelix fold is some way down the wall. When one is doing the drawing on the anterior side of the ear one should not omit to continue the drawing up and over the helix edge. It is then possible to follow exactly the same line as on the anterior side down the posterior side to the middle of the lobule in a curve which follows the antihelix sulcus. The skin to be excised on the posterior side has this curved line as its axis. It is better to make a skin excision with parallel sides and pointed ends rather than an elliptical skin excision as is usually the case. If an ellipse of skin is excised, it can easily

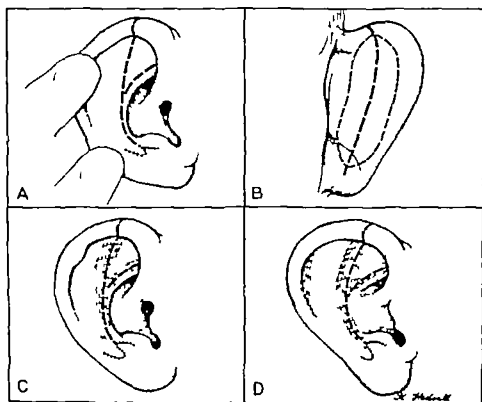


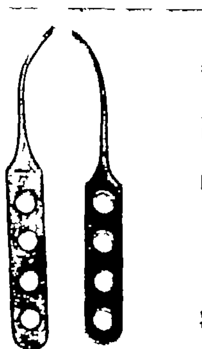
Figure 4. Diagrams showing the operation procedure for prominent ear. A. The ear bent back in order t produce correct antihelix and posterior crus, which are then outlined in dye. B. The outlining on the posterior side of the ear follow corresponding course. The f t re kin excision is drawn in as trip with parallel sides and pointed ends. C. The anterior side of the ar under mined and scrat hed. D. Extra scratching along the h lical fossa in pearshaped ear

result in a tendency of the upper and lower poles of the ear to slip out through the suturing whilst the middle part of the ear may be drawn in Another important thing to remember is that the skin excision should be pretty wide — the more prominent the ear the broader the strip should be. In children, the width of the skin excision should preferably be no less than 1 1/2—2 cm Infiltration of 1/2 % Citanest Exadrin is used for anaesthesia A traction suture in the free edge of the ear facilitates further manipulation and blood is prevented from running down the auditory canal by a gauze sponge plug

The skin excision on the posterior side of the ear should be made very superficial so that it is just a full thickness piece of skin that is taken away In this way the subcutaneous tissue is only slightly disturbed and bleeding is generally insignificant. Mosquito forceps applied to bleeding vessels can be taken away after a few minutes and ligatures are not necessary The risk of postoperative bleeding, which is generally not uncommon in operations on prominent ears, is virtually eliminated So is the postoperative feeling of numbness and paraesthesia

The next step is to expose cauda helicis by undermining along the lower posterior edge of the skin excision. The natural cleft between cauda helicis and antitragus is opened out so that the cauda can be completely freed all round A 1 cm wide undermining over the anterior side of the ear cartilage is then carried out from the open cleft between the cauda and antitragus along the drawn-in antihelix fold and crura

The auricular cartilage is then scratched inside the undermined areas by means of a special instrument (Fig 5) There is one for each side so that the curvature



along the antihelix and crura can be followed. The claws of the instrument are very fine so that scratching can be superficial. Even so it is possible to scratch deeply if the instrument is pressed hard against the cartilage and this may be necessary in the case of an adult with thick, hard cartilage. Nor is it difficult to cut right through the cartilage if a sharp exterior edge is desired. The only place where this is worth trying for is along a badly marked anterior crus — here the sharp fold is simply normal.

All scratching of auricular cartilage is easier to perform if a compress is pressed against the posterior side of the ear. It is easier both to undermine and to scratch the left side ear if the operator stands on the right of the patient.

As was stated above undermining should take place over a width of about 1 cm, and scratching should also be performed over the same width. At times, circumstances might demand even wider undermining and scratching, as for example when too high a rear conchal wall needs to be lowered. In that the upper part of the conchal wall is rounded off and made into a fold — the new antihelix fold — the conchal wall is in fact lowered. Scratching may also be performed in places other than those that have already been mentioned. If for example the helix rim does not curl sufficiently it can be made more marked by scratching on its posterior side. Moreover if the ears have a pronounced pear-like shape, it is not always sufficient to scratch along the antihelix and crura in order to move the ears backwards properly. In such cases, a little extra scratching in fossa helicis produces the additional backward curling of the ear that is required.

It has been stated above that an oval skin excision on the posterior side of the ear results in a tendency of the upper and lower poles of the ear to be forced out in a disturbing way whilst suturing. A skin excision with parallel edges is to be preferred, but even there, it some times happens that the lower pole of the ear protrudes quite a lot. If it is the antitragus that is too prominent, one has to expose it — it is easily accessible from the anterior edge of the skin excision — and reduce it to the required degree. If it is the cauda helicis and the lobule that protrude the prominence is best righted by scratching crosswise over the anterior side of the cauda. Should the ear lobule need setting back still further it is easy to do this by extending the skin excision on the posterior side of the ear further down the lobule.

It should be emphasized particularly that it is quite unnecessary to scratch the auricular cartilage so much that the ear acquires a normal position solely by this means. In fact quite a small amount of scratching is required to produce a slight spontaneous curling of the ear backwards. The rest of the bending backwards to a normal position is effected by the suturing of the skin excision on the posterior side.

To ensure that the wound edges fit well we use mattress sutures. We first close the wound roughly with three sutures and get some idea of what the ear's position will be like. If the backward folding of the ear is clearly insufficient, a further strip of skin is excised along the posterior edge of the excision. It is advisable to make this excision narrow: it should seldom exceed 2—3 mm in width since the folding effect on suturing is powerful. When suturing is completely finished, if one should

presses, for that is not the case at all. On the contrary the paper encourages evaporation. The adhesive tape which fixes the paper keeps the whole dressing steady and in place thus has not the usual tendency of ear dressings to work themselves loose or slide off. The tape also comes in useful when dressings are changed later when we only cut through the tape at the front. The kraft paper has assumed a cupped shape under the elastic bandage and can be folded backwards whilst still being held fast by the tape at the back, which thus acts as a hinge. A new wet dressing is laid in place and the paper cup is folded back like a lid. It is secured by a new strip of adhesive tape which bridges the cut made through the previous piece.

We change the dressings for the first time on the day after the operation, and then as required We do not normally continue to dress the ear for more than a week. If the patient has any reason for having the dressing removed before then, it can be taken away after only four or five days. With other operation procedures, it is usual to continue with some kind of ear protector during the nights for several weeks after the dressing has been removed No such protection is needed with this operation method

We take out the sutures two weeks after the operation, and the patient returns for a final checking after three months.

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EXPERIENCE WITH MEDIASTINOSCOPY

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A total of 150 mediastinoscopies have been performed at the Otolaryngological Hospital, Helsinki University during period of six years. Biopsy specimens were taken in 117 cases: in 93 from the superior mediastinum and in 24 from the middle mediastinum. Pre- and post-mediastinoscopic diagnoses are compared and some special cases described in greater detail. The series include 10 cases with the superior vena cava syndrome. It was due in 9 cases to metastases from carcinoma and in one case to reticulum-cell sarcoma.

Mediastinoscopy first described by Carlens in 1959 has already been adopted in many countries as a valuable diagnostic aid in intrathoracic diseases. According to a number of reports, this examination method has yielded good results everywhere (Carlens, Seppälä, Palva, Maassen, Rink, Koskinen and Linden, Reynders, Jepsen). A total of 150 mediastinoscopies have been performed at the Otolaryngological Hospital, University of Helsinki, during six years, and the number of cases thus examined are steadily increasing

The mediastinum is a space or cavity between the right and left pleural cavities which contains all the thoracic viscera except the lungs. It is divided, according to Fried, into four compartments: (1) superior (2) anterior (3) middle, and (4) posterior (Fig 1)

The superior mediastinum is the region above the plane that joins the sternal angle to the intervertebral discs, between the fourth and fifth thoracic vertebrae.

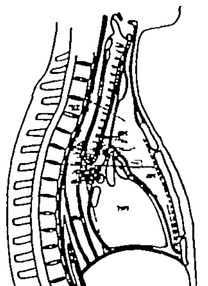


Fig. 1 Diagrammatic division of the mediastinum into four compartments: superior (SM), anterior (AM), middle (M), and posterior mediastinum (PM).

The anterior mediastinum is the space between the sternum and the pericardium which is walled off on each side of the pleurae.

The middle mediastinum contains the heart, the ascending aorta the lower segment of the superior vena cava the bifurcation of the pulmonary artery the bifurcation of the trachea the two main bronchi and bronchial lymph nodes.

The posterior mediastinum is the space between the middle mediastinum and the vertebral column

The pathological changes are mostly located in the superior mediastinum on either side of the trachea Pathological lymph nodes are also fairly often found in the middle mediastinum close to the main bronchi or below the bifurcation These areas are easily accessible by mediastinoscopy

The youngest patient in our series was 14 years old (mediastinal tuberculosis) and the oldest 75 years (pulmonary tumour) The procedure was performed by the Carlens technique using intubation anesthesia. It is worth noticing that the intubation tube also plays an important part in preventing compression of the trachea. In the case of one patient who was in a very low condition local anesthesia was employed. Mediastinal tumours or lymph nodes, if found were liberated with the index finger or a suction tube and a biopsy specimen was removed, in most cases following test puncture and aspiration It frequently proved advantageous to insert fine biopsy forceps through the puncture opening into the tumour and excise the specimen from its interior Hemorrhage in connection with biopsy was thus avoided. Small lymph nodes were occasionally removed *in toto*. A piece of gelatin sponge was invariably placed at the site of the biopsy

A bronchoscopy had usually been made earlier but in 15 cases it was done immediately prior to mediastinoscopy in one and the same anesthesia (bronchomediastinoscopy). Eight patients underwent mediastinoscopy only All the patients examined by mediastinoscopy received antibiotic treatment. The study includes one patient who was pregnant in the third month. Total laryngectomy had been performed in one case because of cancer of the larynx.

There were no major complications In 3 cases, however hemorrhage necessitated the packing of the mediastinum with a gauze tampon which was removed a few days later Left-sided recurrent nerve paralysis occurred in one patient.

The diagnoses made on the basis of earlier examinations are presented in Table 1

The majority of the cases are pulmonary and mediastinal tumours not histologically verified by previous examinations. Mediastinoscopy was performed to reach a definite diagnosis and to avoid exploratory thoracotomy This latter is a bigger operation and more distressing for the patient. The number of cases of suspected sarcoidosis is also considerable.

Anthracotic lymph nodes, grey or black, were found in most cases. They were situated paratracheally parabronchially or below the bifurcation Biopsy specimens were removed in 117 cases. in 93 from the superior mediastinum and in 21 from the middle mediastinum In the former cases, the site of the biopsy was close to the trachea in all except two instances, in which latter the specimens were taken from the anterior part, between the sternum and the large blood vessels (thymoma and carcinomatous metastasis) There are risks involved in exploring

TABLE 1

DI G OSIS BEFO E MEDIASTINOSCOPY

Tumor pulmonis?	15
Tumor pulmonis	35
Carcinoma pulmonis (cum. metast. mediastini?)	1
Tumor pulmonis cum metast. mediastini	13
Tumor mediastini?	18
Tumor mediastini	38
Sarcoma colli (et mediastini?)	1
Adenoma tracheae (et mediastini?)	1
Sarcoidosis?	21
Tuberculosis mediastini?	4
Lymphogranulomatosis maligna?	2
Total	150

the retrosternal region since the veins situated anterior to the arteries are difficult to palpate and can easily be injured There were 84 (90 %) positive biopsies from the superior mediastinum and 12 (50 %) from the middle mediastinum. In the rest of the cases, the lymph nodes were normal or anthracotic.

In 10 cases, the mediastinoscopic findings were positive on the basis of inspection alone. These cases included 5 of old cicatricial or calcified tuberculous lymph nodes, 3 of anomaly or changes in the large arteries, and 2 cases of solid tumour adherent to the aorta

Mediastinoscopy and examination of biopsy specimens in the great majority of cases changed the diagnosis. The post-mediastinoscopic diagnoses are given in Table 2.

Prior to mediastinoscopy diagnosis had been uncertain or inexact in all cases. After it, the diagnosis could be exactly defined in 118 instances (79% of the

TABLE 2

DIAGNOSIS AFTER MEDIASTINOSCOPY

Tumor pulmonis?	8
Tumor pulmonis	20
Carcinoma pulmonis	1
Carcinoma pulmonis *cum metast. mediastini*	40
Tumor mediastini	4
Tumor malignus mediastini	7
Thymoma malignum	2
Sarcoma mediastini	6
Sarcoma colli	1
Carcinoma metast. pulm. posta ca uteri	1
Carcinoma metast. pulm post ca mammae	1
Carcinoma oesophagi et mediastini	1
Struma retrosternalis	3
Adenoma tracheae	1
Haemangioma mediastini	1
Sarcoidosis	23
Tuberculosis mediastini	14
Lymphogranulomatosis maligna	5
Silicosis	1
Lymphonoditis mediastini	3
Sclerosis a. anonymae	1
Aneurysma aortae	1
Anomalia aortae	1
Paresis n. recurrentis sin.	2
Total	150

total) The diagnoses »tumor pulmonis»? (8 cases), »tumor pulmonis» (20 cases) and »tumor mediastini» (4 cases) still remained in doubt. Other subsequent examinations, operations and the clinical course established the diagnosis in these doubtful cases also

Of the 8 cases of »tumor pulmonis?» 2 were recognized as inflammatory processes and 6 as carcinoma, one of which was treated surgically All 20 cases of »tumor pulmonis» proved malignant carcinoma was diagnosed by histological means in 9 cases, one patient was treated by exploratory thoracotomy and 2 by radical operation Two of the 4 cases or »tumor mediastini were solid tumours adherent to the aorta, and no biopsy was made because of the attendant risk of hemorrhage both received radiation therapy Mediatsinoscopy was negative in the other two cases; thoracotomy revealed retrosternal thymoma in one of them, retrosternal goitre in the other These cases show that the retrosternal space is not reached by mediastinoscopy Its upper part, at the most, can be palpated with the index finger if great care is exercised

We see, that the biggest group is *pulmonary cancer* with mediastinal metastases (40 cases) and all these cases were in operable. Mediastinoscopy made the exploratory thoracotomy unnecessary

Our series also includes other tumours. (1) seven malignant tumours which eluded closer histological diagnosis, (2) two malignant thymomas, one of which was cured by radiation whereas the patient in the other case died half a year later from metastases, (3) six sarcomas, i.e. four reticulumcell sarcomas and two lym phosarcomas, (4) 3 retrosternal goitres, (5) a bronchial adenoma in the trachea and (6) a mediastinal hemangioma.

The *adenoma* was of carcinoid type and was found by bronchoscopy in the middle portion of the trachea in a 60-years old man. Mediastinoscopy indicated that the whole tumour was intratracheally situated It was removed endoscopically by electrocoagulation, which resulted in cure.

An unusual mediastinal *hemangioma* was found in the superior mediastinum of a man aged 52. A shadow assumed to represent a tumour had already been detected six years previously and the patient had been at hospital several times because of frequent infections associated with fever Mediastinoscopy showed numerous clots of blood in an extensive area of sclerosing tissue. The patient, who suffered from severe diabetes, died 10 days later from profuse hemorrhage. Specimens for microscopic examination showed capillary hemangioma and autopsy confirmed the diagnosis.

The mediastinum is the typical site of *sarcoidosis* Diagnosis was possible in all the suspected cases except one, which was a case of mediastinal tuberculosis. In subacute sarcoidosis the lymph nodes are large reddish-grey soft, and paratracheally situated. At the chronic stage they are of firmer consistence. Prescalene node biopsy had yielded a negative result in 8 of our cases of sarcoidosis. There were frequently large lymph nodes in the mediastinum in spite of a complete absence of nodes in the cervical region.

Tuberculosis of the mediastinal lymph nodes was diagnosed in 14 cases. Six patients distinctly showed old tuberculous lesions in the lungs and one of these also

had tuberculosis of the cervical lymph nodes. In 3 cases there was caseous material in the lymph nodes, in 5 mainly fibrotic changes, and in 2 calcified areas.

Hodgkin's disease had been suspected in 2 cases but was revealed by mediastinoscopy in 5 cases.

An *inflammatory process involving the lymph nodes* lymphonoditis, remained the sole diagnosis in 5 cases The patients were alive and well 12 months later

Recurrent nerve paralysis occurred in our material in 20 cases, and in one additional case it complicated operation. The cause of the paralysis was disclosed in 17 cases (Table 3)

TABLE 3

CAUSES OF RECURRENT NERVE PARALYSIS

Mediastinal malignancy	13
Mediastinal hemangioma	1
Mediastinal tuberculosis	1
Mediastinal goitre	1
Thyroidectomy	1
Unknown	3
Total	20

The *superior vena cava syndrome* was another important symptom It was encountered in 10 cases and was due in 9 cases to metastases from carcinoma and in one case to reticulum-cell sarcoma. The increased venous pressure causes in these patients oedema and cyanosis of the face, neck and upper part of the thorax. Owing to the collateral circulation there is distension of the veins, and hemorrhage during operation is often profuse. In these patients, however no actual complications due to bleeding occurred. In our experience treatment with diuretics for a few days before operation reduces oedema and the risk of hemorrhage Particular care should be taken when performing mediastinoscopy in cases of superior vena cava syndrome.

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CLINICAL EXPERIENCE WITH MEDIASTINOSCOPY IN BRONCHOGENIC CARCINOMA. A REVIEW OF 500 CASES

O. Jepsen

Århus

Mediastinoscopy a.m. Carlens is a method of exploration and biopsy in the superior mediastinum. A series of 500 cases of verified bronchogenic carcinoma subjected to mediastinoscopy is analysed. The procedure has proved very useful both in establishing a diagnosis and in the assessment of resectability where other conventional methods have failed. A positive mediastinal biopsy will most often render thoracot my superfluous. Negative mediastinoscopy signifies absence of mediastinal m tastases in high percentage of cases. Only few and slight complications were met with in the author's total series of more than 1 000 patients subjected to mediastinoscopy

DISCUSSION

Olavi Koskinen, Joensuu, Finland

The discusser presents a case of asbestosis in tracheobronchial lymph node, diagnosed by mediastinoscopy The X ray examination of th lungs revealed no signs of asbestosis.

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PROLONGED ORO-NASO-TRACHEAL INTUBATION IN CHILDREN

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The maximal period allowed for oro- or nasotracheal intubation without much risk for laryngeal damage has previously been recognised as 24 hours. This conclusion was based on investigations that do not seem to have properly evaluated such factors as laryngeal activity during the period of intubation, material and size of tube, general condition and fl id balance of the patient and finally measures to prevent undue movements of the tube.

In 1962 Brandstat reported the use of oro- or nasotracheal intubation in infants over periods far in excess of 24 hours and without a high incidence of laryngeal damage. Many groups have later used this methods as an alternative t tracheostomy in children. Although different technical recommendations have been given they all have in common, suppression of laryngeal motor activity and voidance of tube-diameter that does not easily fit the larynx and trachea. Humidification must be optimal in order to avoid sticky secretions and blocking of the tube. This method of prolonged laryngeal i tubation as an alternativ to tracheostomy has been used by us during the last tw years. An account of our technique experience and complications will be given.

Previous attempts to determine the length of time for which an oro- or naso-tracheal tube can be left in situ without giving rise to laryngeal damage have shown that the incidence of this complication increases markedly when cases have been intubated for more than 24 hours. These studies, however have not taken into account such relevant factors as the external diameter and material of the tube, the degree of laryngeal muscular activity during the period of intubation and the degree of humidity of the inspired or insufflated air

More recent investigations have shown that when due consideration of these factors is taken, a tracheal tube introduced through the mouth or nose can be left in situ for more than 24 hours without increasing the risk of laryngeal damage.

During the last two years we have used indwelling endotracheal tubes for 24 hours or more in a large number of cases in the Departments of Intensive Care at the University Hospital in Uppsala. In this way we have been able to assist breathing with a ventilator during the first and sometimes even the second post operative days in more than 200 cases subjected to cardiopulmonary by-pass procedures and in about 50 cases where respiratory assistance was required after abdominal surgery in very old or adipose patients. We have also used oro- or naso-tracheal intubation for ventilatory assistance in respiratory insufficiency associated with status asthmaticus or acute exacerbations of chronic pulmonary

This investigation has been supported by the Swedish N tional Association against Heart and Chest Diseases.

disease. During the first two years we have not considered it necessary to tracheotomize any patient with barbiturate poisoning We have had very encouraging experiences with intubation therapy in the neonatal period, when tracheotomy involves particularly great risks.

14 children below 1 year and a further 18 children below 15 years of age have had endotracheal tubes in situ for more than 24 hours. All of these patients had very serious conditions which could account for 11 of them dying during the period under review We have not found or had reason to suspect that intubation has had any deleterious consequences in any of our cases. All the 21 patients surviving (Table 1) were examined immediately after extubation. Follow-up examinations were made after at least 2 months and included laryngoscopy in 18 of the patients. Two others questioned but not available for examination, stated that they had had no symptoms, either respiratory or vocal. No follow-up was carried out on 1 child.

Figure 1 shows. the durations of the intubation periods in different age groups, the lengths of time for which the patients were curarized, whether they had ventilator treatment or breathed spontaneously and also the number of patients in whom tracheotomy became unavoidable after extubation because of difficulties in breathing In the group of children who were under 1 year of age no late complications have occurred in spite of the fact that the intubation periods were longest in these patients

The material of which the endotracheal tube is made should be noninjurious to the tissues and pliable at body temperature if the risk of laryngeal complications is to be reduced. Polyvinyl plastic fulfils both these conditions. Such tubes have been exclusively used in the treatment of 9 children, and in these cases no complications have been noted either in the period immediately following extubation or at the follow-up examination

In order to avoid damage it is very important to use tubes that pass easily through the larynx. The tube should certainly not exert any circumferential

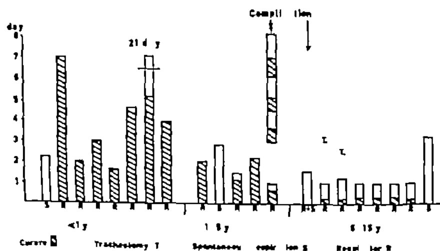


Fig. 1.

pressure on the cricoid ring, for this can give rise to an annular necrosis of the mucosa and may culminate in a cicatricial stenosis. In the first of our two patients who had late laryngeal complications we ascribe the main cause to the fact that in the first 24 hours of intubation the spirally-reinforced tube was too large. Following extubation the patient had increasing stridor and was reintubated with a Portex tube after 18 hours. Furthermore, the laryngeal motor function was not adequately depressed during either the first or second intubation period. Tracheotomy was performed 8 days after the start of the treatment. This would have involved more risk if it had been carried out earlier, as the child had undergone colonic transposition for oesophageal atresia, and the operation wound overlying the trachea had been infected during the initial postoperative period. On extubation, a subglottic swelling and signs of an annular mucosal necrosis could be identified by direct examination. During the healing process a cicatricial stenosis developed at the level of the cricoid ring. Dilatation by passage of probes was achieved on three occasions and the stenosis had began to respond to this within a few months of the acute stage.

In our opinion, depression of laryngeal muscular activity contributes to a reduction in the incidence of complications from trauma, which is caused generally in the arytenoid region, particularly to the vocal processes. D-tubocurarine (Tubarine®), haloperidol (Haldol®) or phenoperidine (Lealgin®) have been used to depress laryngeal activity. The second case in this series to have a late laryngeal complication illustrates the significance of continuing motor function in the causation of the damage described. This patient was a 9 year old boy who had had a severe skull injury followed by epileptiform convulsions. This periodically excessive laryngeal activity led to damage of the vocal processes, followed by healing with the formation of scars and a membranous diaphragm bridging the posterior commissure. These now limit complete abduction of the vocal chords and he had stridor on effort but not at rest.

To prevent secretions forming plugs in the tubes, especially those of fine calibre it is essential that the air be moistened effectively. For this purpose ultrasonic nebulizers are employed, either incorporated into the ventilator circuit or used on the steam tent principle. In two cases where no adequate air moistener has been available, inspissation of secretions in the tube has caused an acute airway obstruction. In both cases, the tube was changed and suction performed immediately after occurrence of the blockage.

Chest radiography was performed daily during the period of intensive care. Two patients were intubated and ventilated because of respiratory insufficiency attributable to an extensive pulmonary infiltrative condition which, however, regressed markedly during the intubation period in both cases. One further patient had a broncho-pneumonic consolidation at the beginning of the treatment, but this had disappeared before extubation was performed.

In 8 cases, dense patches were seen, mostly attributable to atelectasis, and in the others the radiographs were normal.

In 5 cases the larynx and trachea were examined macroscopically at necropsy (Table 2), but there were no findings of ulceration or necrosis of the mucosae

TAB-

REHABILI

	Age sex	Diagnosis	Intubation			Tube	
			oral	nasal	period	internal diameter	material
							Postoperative
1964	12 years \ AM ♀	Coarctation of the aorta	+		21 hrs	7.5 mm	Armoured rubber
1965	14 years M LO ♀	Atrial septal defect	+		28 hrs	7 0 mm	Armoured rubber
	12 years GK ♂	Fallot s tetralogy	+		21 hrs	7 0 mm	Armoured rubber
	13 years EE ♀	Aberrant Pulmonary veins	+		24 hrs	8.0 mm	Armoured rubber
	12 years AL ♂	Fallot s tetralogy	+		24 hrs	7.5 mm	Armoured rubber
	15 years KS ♀	Atrial septal defect	+		21 hrs	8.0 mm	Armoured rubber
	3 months PS ♂	Supraglottic submucous cyst.		+	47 hrs	3.5 mm	Portex
	4 years ME ♀	Fallot s tetralogy	+		32 hrs	5 mm 4.5 mm	Armoured rubber Portex
	1 day K EM ♂	Myelomeningocoele		+	69 hrs	3.0 mm	Portex
1966	1 month GJ ♀	Pulmonary stenosis	+	+	37 hrs	3.0 mm	Portex
	1 ½ year JE ♂	Oesophageal atresia	+	+	6 days	4.5 mm	Armoured rubber
	12 years IN ♀	Portal hypertension	+		74 hrs	7.5 mm 5 0 mm	Rubber Portex
	1 ½ month DD ♂	Transposition of th great vessels	+		21 days	3.5 mm	Rubber Portex
	10 days KD ♂	Transposition of the great vessels		+	80 hrs	3.0 mm 3.0 mm	Armoured rubber Portex
							Mixed
1964	8 months LJ ♂	Encephalo trigeminal angiomatosis with convulsions	+	+	55 hrs	3.5 mm 4.5 mm	Rubber Portex
	9 years GE ♂	Head injury with convulsions	+		38 hrs	6.5 mm	Rubber
1965	5 months A LP ♀	Reticuloendothelioma	+		7 days		Portex
	3 years IS ♂	Acute epiglottitis	+		46 hrs	3.5 mm	Portex
	5 years LN ♀	Head injury with unconsciousness	+		64 hrs	6.0 mm 5.5 mm	Portex
	4 years SA ♂	Acut epiglottitis	+		53 hrs	5.0 mm	Portex
1966	3 months J ♀	Prematurity Pneumonia	+		112 hrs	3.5 mm	Portex

LE 1
TATED

group

Respirator	Muscular relaxants	Primary development	Follow up (oice and laryngoscopic findings)
+	Tubarin (6 hrs) Lealgin (3 mg)	Subglottic oedema 2 days after extubation — tracheostomy	Normal
+	Tubarin (6 hrs) K logan + Lealgl	Strid lous respiration after extubation — tracheostomy	N complaint Good singer (Larynx not examined yet)
+	Tubarin (8 hrs) Lealgin (4 mg)	Normal	—
+	Tubarin (8 hrs) Lealgin (7 mg)	Normal	Normal
+	Tubarin (9 hrs) Lealgin (3 mg)	Normal	Normal
+	Tubarin (6 hrs) Lealgin (8 mg)	Normal	N complaints (Larynx not examined yet)
+	T barin	Normal	Normal
+ — (8 hrs)	Tubarin (— 8 hrs)	Laryngoscopic findings at extubation essential normal Respiratory inadequacy — tracheostomy	Normal
+	T barin	No respiratory difficulties. Moderate fibrin coating in the subglottic region	Normal
+	Tubarin	Normal	Normal
+	Tubarin (periodically) Haldol (11.5 mg) Lealgin* (7.4 mg)	Subglottic oedema — tracheostomy	Subglottic stenosis
—	Lealgin (2 mg) Haldol (10 mg)	Essentially normal	Normal
+	Tubarin (5 days) Lealgin (10.2 mg) Haldol (3.75 mg)	Moderate oedema in the arytenoid region	Normal
+	Tubarin Lealgin (1.3 mg) Haldol (5 mg)	Normal	Normal

group

Respirator	Muscular relaxants	Primary development	Follow up
—	—	Extubation difficulties — tracheostomy for 3 weeks	1 month fter extubation no signs of laryngeal damage Slight hoarseness
+ —	Azacon	Stridulous respiration post extubation — tracheostomy	W b m the posterior commissure Slight signs of te-nosis
+	T barin	Normal	Normal
+	Tubarin Lealgin (8 mg)	Normal	Normal
—	Haldol (6.25 mg) Pethidin (20 mg)	Normal	Normal
+	Tubarin Haldol (18 mg)	Normal	Normal
+	Tubarin	Normal	Normal

TAB

DIED WHILE

Postoperative

ıg Sex	Diagnosis	Intubation			Tube	
		oral	nasal	period	internal diameter	material
day ♂	Oesophageal atresia	+		60 hrs	3.5 mm	Rubber Portex
days J ♀	Oesophageal trcsia	+		48 hrs	3.5 mm	Portex
day A ♂	*Oesophageal atresia with tracheo-oesophageal fistula*		+	*36 hrs*	*3.5 mm*	*Portex*
years J ○	Transposition of the great vessels	+		40 hrs	5 mm	Armoured rubber
years S ♂	Ebst in s disease	+		26 hrs	6.5 mm	Armoured rubber
month ♂	Fallot t tralogy	+		24 hrs	4 mm	Portex
½ year F ♀	Cerebral oedema		+	55 hrs	4 mm	Portex
						Mixed
½ year B ♂	Head injury with unconsciousness	+		5 days	4.5 mm	Arm ured rubber
years N ♂	Head injury with unconsciousness	+		61 hrs	*7.5 mm*	Rubber Portex
m nths S ♀	Encephalomeningitis		+	6 days	3.5 mm 4.5 mm	Portex
month ♂	Sepsis		+	54 hrs	2.5 mm 3 mm	Portex

one child, who died of septicaemia, there was a generalised redness of the ıchea and larynx

Our experiences gained with the treatment of patients in this briefly presented ies can be summarised as follows. —

Portex tubes of polyvinyl plastic have been found to produce much less damage an rigid rubber tubes The shape of the plastic adapts to the natural curves at dy temperature, and it is much less irritating to the mucosae.

It is important to choose a tube that does not stretch the larynx or exert circum-ential pressure in the cricoid region. This is particularly important when treating all children, but has the disadvantage that the internal diameter of the tube ll be small and the airway resistance correspondingly high.

Adequate humidification of inspired air preferably by an ultrasonic nebulizer then even more necessary to prevent plugging by inspissated secretions. Further ore one should always be prepared for changing the tube immediately when the ed arises, and in children it should be changed routinely once a day when the rynx should also be inspected.

The laryngeal motor function must always be depressed, and when this is to be

LE 2

INTUBATED

group			
Respirator	Muscular relaxants Sedatives	Cause of death	Post mortem examination
+	—	Oesophageal atresia Truncus arteriosus Heart failure	—
+	—	Oesophageal atresia	—
+	Tubarin	Oesophageal atresia Congenital heart disease	
+	Tubarin	Heart failur	Macroscopic normal findings
+	—	Heart failur	Macroscopic norm l findings
+	Tubarin	Heart failure	—
+	—	Cerebral oedema	Macroscopic normal findings
group			
+	—	Cerebral injury	—
+	—	Cerebral injury	—
+	—	Encephalomeningitis	Macroscopic normal findings
+	Valium Phenemal	Sepsis	Macroscopic slight swelling of the larynx and the trachea

combined with artificial ventilation we achieve both these aims most conveniently by intermittent administration of phenoperidine (Lealgin®) to adults whilst preferring d-tubercurarine (Tubarine®) for children. When spontaneous breathing is indicated or desirable the patient, usually a child, is sedated with haloperidol (Haldol®)

As a rule children should be intubated through the nose and the wider nasal passage should be chosen. We have usually used oral intubation in adults, who generally have a nasal passage considerably smaller in relation to the larynx.

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1 month—1 year (infants) and 1 year—16 years. With respect to duration o[f] intubation the patients were divided into two main groups, one consisting o[f] those intubated less than 24 hours and the other of those with prolonged intuba-tion. The latter of course, form the most interesting part of the series. The mai[n] figures in the »total» column at right refer to the patients with prolonged intuba-tion, the figures in parentheses show the corresponding totals in the whole series.

From table 1 we see that children aged 0—1 months, i.e. the newborn, form the majority: their total number in the prolonged intubation groups is 82 and in the whole series 150. This is quite natural, since the conditions leading to dif-ficulties in respiration are manifested especially at birth or soon thereafter. The duration of intubation has not exceeded 24 hours in 98 of the 225 patients, while the prolonged intubation group comprises 129 patients. Of the latter 108 were intubated for 7 days or less. In 8 patients the intubation lasted for more than 14 days; 7 of these were in the newborn group. One of these children had a giant sized cystic cervical hygroma, which was operated on several times (fig. 1). In this case the intubation was maintained for 55 days, after which tracheotomy was per-formed. It is noteworthy that the unusually long duration of intubation caused no permanent changes in the laryngeal mucosa. However, some softness of the cartilage was observed, which did not affect natural respiration and which may wholly or in part have been caused by the hygroma.

Table 2 presents the percentages of cases in the various age groups in which intubation was interrupted and substituted by tracheotomy. In the group of 150 newborn infants this was necessary in 7 cases only (5 per cent). The usual reason in these cases was oedema caused by the tube, accompanied in some instances by erosion of the laryngeal mucosa. In one case only the tracheotomy was made necessary by the basic disease, macroglossia. The percentage of tracheotomies in the older age groups was higher than among the newborn, especially in the patients over 1 year of age. This was mainly due to the fact that the risk



Fig. 1. A newborn baby with a large cystic hygroma. Tracheotomy was performed after pro-longed intubation of 55 days. The patient was successfully decannulated at the age of 1 year 8 months.

TABLE 2

NUMBER OF INTUBATIONS AND TRACHEOSTOMIES IN DIFFERENT AGE GROUPS

Age	Total number of intubations	Tracheostomies	
0— 1 month	150	7	5 %
1—12 months	38	7	18 %
1—16 years	37	15	41 %
Total	225	29	13 %

TABLE 3

LATE RESULTS OF TRACHEOSTOMIZED PATIENTS

Age	Tracheostomies	Deaths	Decannulated	Still with tracheostomy
0— 1 month	7	2	5	—
1—12 months	7	4	3	—
1—16 years	15	1	12	2
Total	29	7	20	2

TABLE 4

DEATHS OF INTUBATED PATIENTS

Age	Number of intubations	Deaths	
0— 1 month	150	82	55 %
1—12 months	38	12	32 %
1—16 years	37	9	24 %
Total	225	103	47 %

of laryngeal complications caused by the cannula is not as great in these children as in the newborn. The indications for tracheotomy among the older children were therefore wider than in younger groups. Thus in the group of children over 1 year of age the indication for tracheotomy was laryngeal complication in one case only; in the other cases the tracheotomy was always called for by the basic disease.

In addition to the laryngeal complications mentioned above which made tracheotomy necessary, the tube in some cases caused irritation of a mild degree which did not necessitate tracheotomy. All in all the intubation was observed to have produced severe or moderate irritation of the larynx in only 11 of the total 225 patients.

The fate of the 29 tracheotomized patients is seen in table 3. Seven have died, 20 have been successfully decannulated and 2 continue to carry the cannula. The cause of death in 4 cases was suffocation caused by profuse accumulation of mucus in the respiratory tract or by constriction of the trachea below the tracheostoma, and in 3 cases death was due to the basic disease.

The mortality among the intubated patients is shown in table 4. The average was 47 per cent in the total series and 55 per cent in the newborn group. It should be noted, however, that in the majority of these cases death would most probably have occurred without the active treatment.

Table 5 shows the distribution of the patients by the basic disease which called

TABLE 5

CAUSES OF INTUBATION AND DEATHS ACCORDING TO DIAGNOSIS

Cause of intubation	Number of intubations		Deaths		
)perated thorax cases		46		12	26 %
— atresia oesoph.	17		6		
— vitium cordis	23		6		
)ther operated cases		35		13	37 %
— hernia diaphr	6		1		
— atresia duodeni	10		3		
— hydrocephalus	5		3		
Not oper respir diseases		91		47	52 %
— RDS	39		15		
— laryng. pseudocrup.	2		—		
— haemorrh. pulm.	9		9		
Respir insuff of other not oper cases		53		33	62 %
— vitium cordis	10		10		
— haemorrh. cerebri	16		15		
— myopathia	4		1		
Total		225		105	47 %

TABLE 6

ARTIFICIALLY VENTILATED PATIENTS IN DIFFERENT AGE G UPS

Age	Number of ventilated		
	Manual	Respirator	Total
0— 1 month	122	4	126
1—12 months	29	8	37
1—16 years	6	22	28
Total	157	34	191

›r intubation, and a corresponding distribution of the deaths. Thoracic surgery as the reason in 46 cases and other surgical measures in 35 cases. The largest umber of intubated patients, totalling 91 falls within the group of respiratory iseases in the non-operated cases, the most common diagnosis being RDS espiratory distress syndrome or hyaline membrane disease of newborn) Respira-›ry insufficiency not caused by the pathologic condition of the respiratory organs ut by e.g., heart disease, cerebral haemorrhage or myopathy was the indication ›r intubation in 53 cases. The highest mortality 62 per cent, occurred in this roup. It seems probable that very few if any of the patients in this group would ave survived without intubation or tracheotomy and artificial respiration.

Most of the intubated patients, 191 out of 225 (table 6) required artificial respira ion given manually or with a respirator of Engström or Blease model. Table 6 hows the number of ventilated patients and the length of ventilation in each age roup Comparison with table 1 indicates that the need of ventilation, expressed a percentage, was approximately as frequent among the newborn as in all the ther groups together Manual ventilation predominated in two youngest age roups, while the respirator was more often used in treating the older patients, circumstance that is quite natural.

TABLE 7

DURATION OF VENTILATION IN DIFFERENT AGE GROUPS

Age	Duration of ventilation			
	<1 day	1—14 days	>14 days	Total
0—1 month	68	54	4	126
1—12 months	14	10	4	37
1—16 years	11	11	6	28
Total	93	84	14	191

The duration of ventilation (table 7) was longer than 14 days in only 14 of the 191 cases. 93 patients were ventilated for a shorter time than 24 hours, and 84 patients for 1—14 days. Of the latter not less than 75 patients were ventilated for 1 week at the most, and only 9 for 1—2 weeks.

With the exception of the cases in which the intubation was performed for anaesthesia and the tube left in place after the operation, the patients usually were intubated without anaesthesia. However if the tube irritated the patient we occasionally used an analgetic and even relaxation. We have been particularly satisfied with sedatives that are used in neuroleptic anaesthesia.

In most cases we have used Magill's red rubber tubes for the intubation. Our experience with Portex tubes is limited. The intubation has generally been performed orally but recently the tube has been introduced nasally in about a dozen cases. The orally inserted tube has been changed daily and in this connection the bronchial toilet has been done. The nasally inserted tubes have been retained without interruption for 1—2 weeks when necessary. Active physiotherapy clapping, change of position and suctioning of the respiratory tract, as well as humidification of the inspired air are obligatory in the treatment.

Discussion and Conclusions

Tracheotomy in children quite frequently causes oedema in the area between the tracheostoma and the glottis and erosion in the trachea. Decannulation is in many cases associated with great difficulties, especially in small children, and in some individual cases it has been necessary to postpone removal of the tracheal cannula for so long that the child grows up. On the other hand, intubation seldom gives rise to laryngeal irritation of such degree that the respiration after removal of the tube is threatened and tracheotomy becomes necessary. A postoperative respiratory insufficiency is easily managed by prolonged intubation, and difficulties in respiration due to other causes can also be treated in the same manner at least in the early stage. If tracheotomy is later necessary it can be carried out without haste, avoiding emergency tracheotomy.

Our experiences have convinced us that in cases of respiratory difficulties in children, particularly in small children, the treatment of choice is intubation, which in most cases can be prolonged, and that tracheotomy should be performed only when, for some reason, intubation cannot, or should not be continued.

DISCUSSION

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For one and a half years I have had the good fortune to participate as a consulting laryngologist, in the treatment of children with difficulties in breathing at the Children s Hospital, University of Helsinki. During this period I have become increasingly convinced that we laryngologists are insufficiently acquainted with this field. Few of us know much about the questions dealt with by Dr Suutarinen in his paper and we may be mightily surprised that children can remain intubated for days, even weeks, without any permanent damage arising, provided the condition f the larynx is carefully watched.

A large proportion of the infants needing intubation are poorly developed and too weak to breathe spontaneously so they must be given artificial respiration. These infants, newborn in particular must be treated in the intensive-care unit of a pediatric hospital. But it seems advisable to treat also other cases of respiratory difficulties in young children at an up-to-date pediatric hospital rather than at an otolaryngologic hospital.

In these cases, the anesthesiologists play an essential part, and success depends decisively on their interest, knowledge and skill. Dr Suutarinen is an anesthesiologist and to him belongs the credit for the standard achieved in the Children s Hospital in the field concerned.

In this connection I should like to say something about our method of *decannulating young children fter tracheotomy* Should decann lation not succeed without special measures, the hild is given cortisone for a couple of days and is transferred after conventional preoperative care, to the surgical division for decannulation. Anesthesia is induced the cannula removed and respiration is supervised. If difficulties arise at the time the baby begins to recover from anesthesia, this is prolonged rectally In a few cases, rectal anesthesia was continued for 2—3 days during which cortisone was administered. Decannulation may succeed in this way even though the condition ppears desperate at initial recovery from anesthesia If reinsertion of the cannula is necessary we usually first widen the tracheostoma using oesophageal probes for infants and introduce a small anesthetic tube through the thus enlarged opening. The baby is allowed t breathe through this tube for a while before introduction of the cannula.

The number of long-term cannula-wearers has been reduced to a minimum as compared with the situation a few years ago, by using these measures: prolonged intubation and avoidance of tracheotomy whenever possible decannulation by the method here outlined in those cases where tracheotomy proves, after all, inevitable.

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Diamant to Björk

There is a group for which it is of particular importance that tracheotomy should not be performed. patients suffering from poisoning d e to barbiturates. In this connection it is often matter of treating patients with depression, nd a scar remaining after tracheotomy can act as a eminiscent tigma.

Cases of acute supraglottic laryngitis, i.e. epiglottitis, may undoubtedly be treated most advantageously by applying intubation instead f performing tracheotomy In most cases intubation does not require treatment for more than two days. The suitability of this method is more doubtful, however in subglottic laryngitis, especially if tracheitis is also present.

A regards decannulation in small children, this can prove very difficult as Professor Björk has pointed out. Subsequent decann lation can be facilitated by using what is known as dunda-näsa Besides moistening the air-passages, this artificial nose also produces a resistance which partly corresponds to that in the nose and larynx. The sensation of respiratory obstruction is very slight when the cannula with the device is removed.

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It will be interesting f course to hear in the f ture about possibilities fo prolonged intubation in acut infections of the larynx and trachea. I only wish to call to mind here the long experience of our older colleagues with int bation in cases f diphtheria with tru croup They were ble largely to cope w th these grave laryngeal infections by intubating the patient for several days.

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FOREIGN BODIES IN THE LOWER RESPIRATORY TRACT

A STATISTICAL REVIEW

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The material includes 65 suspected and 155 verified cases of foreign bodies in the lower respiratory tract treated at the Department of Otolaryngology of the Helsinki University Central Hospital in the years 1918 through 1962. The percentage of male cases was 57 The majority of patients were children under school age (80 per cent). Less than two-thirds of the foreign objects were of organic origin. Most frequently it was nut or seed, the next common group was made up of needles. An ample half of the foreign bodies were located in the main or stem bronchi, the ratio right: left being 76/39 Classic symptoms: dyspnea and attacks of coughing, and the more so the upper the location of the foreign object, were present each in about 60 per cent of the total material. Half the patients were free from symptoms when admitted to hospital, one-fourth were affected by evident dyspnea and only in 4 per cent an emergency was concerned.

Removal of the foreign body was successful by endoscopy in 92 per cent (143 cases) In only one of the remaining 12 cases there was an organic foreign body Six of these patients were remitted for thoracotomy to the Department of Thoracic Surgery

The majority of patients rapidly recovered after removal of the foreign body In about 10 per cent of cases tracheostomy had to be performed postoperatively Two cases of fatality occurred.

During the fifteen years between 1918—1962 155 cases of foreign bodies in the larynx, trachea and bronchi were treated at the Department of Otolaryngology of the Helsinki University Central Hospital. In addition, there were 65 suspected but unverified cases of a foreign body Consequently our whole material consists of 220 cases, of which a foreign body could definitely be diagnosed in 70 % of the cases.

The number of patients with a verified foreign body varied between 6 and 16 yearly The corresponding figures in the group of the unverified cases were between 0 and 11

Table 1 shows the age and sex distribution of the material. Boys are in majority in all age groups of those below 14-year-old. Among the 155 verified cases 57 % are male, and in the group of the unverified cases the percentage is still higher 62 %. A great majority of the patients, 80 %, were below school age (Kassay 1960 75 %, Mounier Kuhn 1966 79 %)[1] and 92 % of them were below 15 years of age.

Table 2 illustrates the quality of the foreign bodies. Of these 60 %, or 91 out of a total of 155, were of organic origin, i.e. belonged to the vegetable or animal

[1]) Figures calculated by the authors

TABLE 1 AGE AND SEX DISTRIBUTION OF 155 VERIFIED AND 65 SUSPECTED CASES OF RESPIRATORY FOREIGN BODY

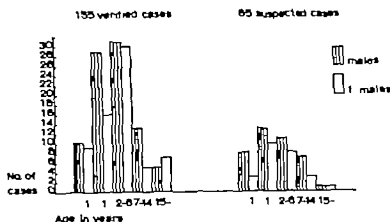


TABLE 2. THE QUALITY OF 155 VERIFIED AND 65 SUSPECTED FOREIGN BODIES OF THE LOWER RESPIRATORY TRACT

	VERIFIED	SUSPECTED
ANORGANIC SUBJECTS		
Needles	22	0
Sc ews spikes t	18	0
Stones,pearls, coins t	8	2
Others	13	5
Total	61	7
ORGANIC SUBJECTS		
Nuts seeds,pea et	42	13
Pi es of fru t or vegetabl	16	15
Head of corn sprig of f tc	20	4
Fishbone bone etc	11	0
Pieces of meat bread t	3	12
Others	2	2
T tal	94	46
QUALITY UNKNOWN	0	12
TOTAL	155	65

groups. The remaining 40 %, or 61 foreign objects, were inorganic, i.e. made of metal, stone, plastic, etc. Jackson and Jackson 1950 report in their series about 40 metal objects; Mounier Kuhn et al. 1966 about 36 % metallic or plastic; and Kassay 1960 29 % unorganic foreign bodies.

The most common group in our material is made up of nuts, seeds, peas, etc., which were found in 42 cases or more than a quarter of the total, 27 %. The second largest group consists of various needles and pins (22 cases or 14 %), and the third largest group contains corn and grass heads, spruce sprigs, etc., which were found in 20 cases or 13 %. Other common objects were screw and nails, pieces of fruits, carrots, and fish-bones.

When examining the group of the unverified foreign bodies we could observe that the part of the organic foreign objects was even greater 42 cases out of 65

(about 71 %) On the other hand the part of the inorganic foreign objects was considerably smaller only 7 cases out of 65 (about 10 %). Apart from these, there were 12 cases in which we could only suspect a foreign body of unknown origin in the lower respiratory tract.

Further it is interesting to notice in our material that in all cases in which a corn or grass head, fish-bone, needle, or screw had been indicated as a possible foreign object a positive diagnosis could always be reached, and the foreign object verified. On the other hand, the finding was positive in only 3 cases out of 15 when a piece of bread or meat was suspected as a foreign body The foreign bodies of inorganic origin were distributed fairly evenly between different age groups whereas those of organic origin were concentrated to the younger patients. About 88 of the latter were found in patients below 7 years of age. Only 69 % of the inorganic foreign bodies were found in this age group The eleven cases of a corn or grass head in our material belonged to these age groups, and eight of these children were below the age of one year

The localisation of the verified foreign bodies corresponded to what was to be expected. This is shown in table 3 Three quarters of all the objects were located in the bronchi 58 % in main or stem bronchi, and 19 % farther in the periphery In Holinger's material 1962 the percentage is somewhat higher 88 %[1]). Kassay 1960 and Mounier-Kuhn 1966 report still higher figures for bronchial location, but have no laryngeal foreign bodies included in their series. The most common site was the right main or stem bronchus (37 %).

TABLE 3 LOCATION OF 155 VERIFIED RESPIRATORY FOREIGN BODIES

	RIGHT		LEFT	UNKNOWN	TOTAL
LARYNX		14			14
TRACHEA		20			20
MAIN OR STEM BRONCHI	58		27	1	86
PERIPHERAL	18		11		29
UNKNOWN			1	5	6
TOTAL	76	34	39	6	155

The right-hand side dominates clearly over the left-hand side, as is indicated by the figures 76 were on the right 39 on the left-hand side, the ratio being 1 95 (Holinger 1962 1.62, Mounier Kuhn 1966 1 46)[1]) As it was to be expected, the location of the inorganic foreign bodies was deeper in the bronchial tree than that of the organic ones. The portion of the inorganic objects rises from 20 % in the larynx to 55 % in the periphery

From the anamnestic data we most often gathered two initial symptoms: an attack of coughing and dyspnoe Both were present in about 59 of the 155 cases of verified foreign body Other common symptoms were cough of long duration

[1]) Figures calculated by the authors.

(45 %) fever (29 %), and cyanosis (17 % of the patients). The symptoms varied considerably according to the location of the object and naturally also according to the time passed since the onset of the symptoms. If the patient was treated early the more chronic symptoms such as fever were not yet present. The frequency of cough attacks in the data was quite stable, varying from 50 % to 60% according to the location. The figure was highest in patients with a foreign body in the trachea. The frequency of dyspnoe varied more being 85 % in cases of a foreign body in the trachea, but only 41 % in cases in which the object was located in the periphery around the stem bronchi. Hoarsness was naturally most common (64 %) in cases in which the objects was in the larynx. It was found in only 15 % of the cases containing a foreign body in the trachea. Cyanosis was also found most often in these cases. More chronic symptoms, cough and fever were the more common the farther in the periphery the object was located

The frequency of the occurrence of the symptoms was the same in the 65 cases in which no foreign object could be found. There was one exception, cyanosis, which these patients had in 26 % according to the data, but only in 17 % of the cases in patients with a verified foreign body This may be due to a hazard, but

TABLE 4. MAJOR COMPLICATIONS IN 155 VERIFIED AND 65 SUSPECTED CASES OF RESPIRATORY FOREIGN BODY

	Total number of cases	Verified				Suspected
Period	1948 62	1948 52	1953 57	1958 62	1948-62	1948-62
No of cases	220	47	49	59	155	65
Trachectomy	20	8	5	4	17	3
Removal not successful	12	4	0	8	12	
Deaths	2	2	0	0	2	0

it might also be possible that the foreign object has been in the glottis and has been removed when the patient has been coughing, instead of being inhaled.

Just about half of the patients came to the clinic within 24 hours from the onset of the symptoms. Two thirds came within the first week, and about 6 only after about a month had elapsed. This applies to patients with a verified foreign object. Patients with a negative finding came as a rule earlier to treatment The longest period of time after the onset of the symptoms was four years and three weeks

The general condition of the patient was as a rule good upon his arrival to the clinic. In 20 of the cases of a foreign body the patient had dyspnoe or cyanosis. Seven cases, about 4 %, could be considered emergency cases, and the treatment was begun immediately

Altogether 172 tracheo-bronchoscopies and 8 laryngoscopies were performed in these 155 cases of a foreign body The extraction was successful in 143 cases,

about 92 %, of which in 6 cases, about 4 %, the patient himself coughed out the object. Thus the foreign object remained in the respiratory tract in 12 cases, about 8 %. To six of these patients a thoracotomy was performed elsewhere immediately, to two others later: one patient coughed out the object the day after leaving the hospital, one patient gets on well with the object in the respiratory tract, and the two last patients have not been reached. Ten of these twelve patients had a needle in their respiratory tract. It is interesting to notice that in nine cases of an inorganic foreign body the extraction failed with the first try and was successful in only one renewed bronchoscopy.

In 20 cases (9 %) a tracheostomy had to be performed, in 6 cases together with an endoscopy and in 14 cases later due to post-operative breathing difficulties, and most often within 24 hours. The frequency of the tracheostomy seems to be more closely related to the location of the foreign body than to its quality. The highest frequency, about 20 %, was in patients with foreign bodies in the larynx or the trachea. It was about 10 % in cases of foreign bodies in the main or stem bronchi, and only 3 in cases of foreign bodies in the periphery. Three of these twenty patients to whom a tracheotomy had been performed had no foreign object.

Complications of the lungs were reported in 7 cases out of 155 (about 5 %): 3 cases of pneumonia, 1 of empyema, 1 of pneumothorax, 1 case of post-operative bronchial stenosis and 1 case of bronchiectasy. The frequency of complications has considerably diminished during the last few years as we can see from e.g. the figures for tracheotomy.

Lethality was 1.3 %, two cases out of a total of 155. One was in 1949 and the other in the year 1950. The first patient was a 10-month-old boy with a 4 cm long piece of a corn head in the left-hand-side bronchus of the lower lobe. The cause of death was suffocation and severe tracheobronchitis. The second patient was a one-year-old girl with a rock in the right-hand side main bronchus. Death was caused by severe anoxy due to the foreign body and mucus in the lower respiratory tract. Apart from these, there was one case of death in 1950 in the group of patients with no foreign object. The patient had tracheobronchitis after the bronchoscopy: she had to be tracheotomized, was better and was decannulated. However she again had difficulties in breathing and was suffocated before the cannula could be replaced.

The average time of treatment has clearly shortened during these fifteen years. During the first five year-period 1948—1952 it was about 14.4 days, but during the last five-year period only 8.8 days. The reason is that infections in connection with a foreign body have decreased, with relation to both their number and quality.

We have not been able to show any clear correlation with the length of the history and the frequency of more important complications in this material.

One important point is that in 26 cases, about 17 %, the first doctor that the patient saw had not been able to reach the right diagnosis even if the typical symptoms, attacks of cough and dyspnoe, and later cough of long duration and fever were present.

We have also tried to analyze the way the foreign object has been inhaled, but this has been impossible in retrospect in many cases. However it is noteworthy

TABLE 2

AGE DISTRIBUTION OF 136 PATIENTS WITH FOREIGN BODIES IN THE LOWER RESPIRATORY TRACT. ABSCISSA: AGE OF THE PATIENTS. ORDINATE: NUMBER OF PATIENTS. BLACK COLUMNS: NUTS. STRIPED COLUMNS: OTHER FOREIGN BODIES

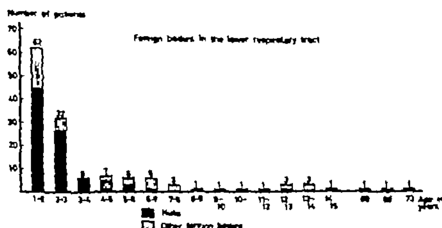


TABLE 3

Complications	Number of patients
Atelectasis	11
Pneumonia	4
Laryngeal edema (including 1 patient with fibrinous tracheobronchitis and mediastinal emphysema)	4
Total	19

More attention should be given to the prophylaxis against aspiration of foreign bodies. Jackson (1) states that 90 per cent of peanut aspirations occur in children, and that this is due to imperfect mastication because the molar teeth have not erupted. He warns against giving nuts to children under 3 years of age. Based on our observations, the warning should be extended to include children less than 4 years of age.

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MICROCIRCULATION IN MUCOUS MEMBRANES OF RESPIRATORY AIRWAYS

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Microvascular architecture and function has been analysed by direct microscopy in vivo in the upper respiratory tract of rabbits in order to clarify the possible connections between microcirculatory disturbances and different kinds of disease and injury in the mucosa. Different kinds of intracapillary phenomena which occur in tissue injury are described.

Surprisingly little attention has been paid to the circulation in the tracheal mucosa in spite of the importance the subglottal airway has to the maintenance of adequate moisture and temperature of the inspired air. The mucous membrane of the nose seems to take the most active part in this function but even the mucous membrane of the remaining respiratory system is said to be essential (Moritz and Weisiger 1945). In the sixties many works have been published where attempts have been made to analyse vascular architecture of the tracheal mucosa from studies with injection technics in animals. In spite of the information being relatively static detailed circulatory dynamics have been discussed.

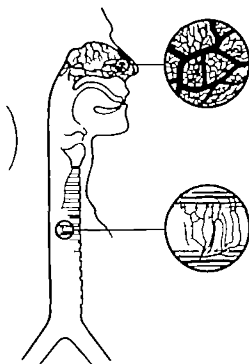
By means of vital microscopy I have tried to clarify the topography and flow properties of the microvascular system in the septum of the nose and in the trachea. This information must be a base for further microcirculatory analyses of this system. The work has been performed on rats and rabbits anesthetized with Nembutal in a Leitz intravital microscope in transmitted light and with equipment for microcinematographic registration and corpuscular flow determination.

A comparison between the microvascular architecture in the nose and in the trachea shows that the former is dominated by venous systems with sinusoid function in places (Messerklinger 1948, Naumann 1960—61). Venules are also seen in trachea, but they are not so dominating. Here a capillary network lengthwise the trachea is found and at the beginning of these capillary loops arteriovenous shunts are often seen. The distance between the true capillaries and the epithelial layer is remarkably little. This may explain the vulnerability of these vessels at the experimental preparation.

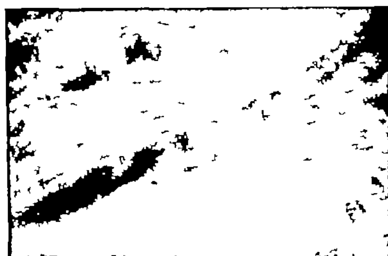
The arterioles and venules often take a course perpendicular to the true capillary bed and are situated in the intercartilaginous spaces. The capillary loops are thus found inside the cartilage rings. Most of these facts have also been described on injection preparations by Sobin et al 1963.

The corpuscular flow velocity is comparatively high in all kinds of vessels (venules 0.4—0.6 mm/sec; arterioles 1.5—2.0 mm/sec). This corresponds well to the presumed function of this vascular bed, namely as a regulator of air temperature.

In our clinical work we daily expose these mucous membranes to various kinds of pharmaca. I'll like to present some preliminary studies in this field.



1 Schematic outlin Illustrating the fundamental differences in vascular architecture between nasal and tracheal mucosa.



2. Arteriole in tracheal mucosa (×350).

Tetracain (2 %) applied on nasal mucosa for up to 20 minutes did not show any changes in flow velocity or vessel caliber If however Epinephrine was added to the solution (4 1) a pronounced arteriolar contraction was noticed. On the venous side a reduction in caliber could also be seen. This later effect was, however not so remarkable. Firstly the corpuscular flow velocities slowly raised in the whole vascular bed. In these places where a distinct injury to the surface epithelium

were clearly visible a congestion of flow was found within a few minutes after application The cessation of flow in these areas was irreversible and a leakage of blood corpuscles was found in places These findings indicate a pronounced tissue injury

If Tetracain was applied to the tracheal mucosa no microcirculatory effect was visible.

When a solution of Tetracain and Biogan (4 1) was used the vascular effects seemed to be of the same degree as when Epinephrine was used as a constringent. In no case however signs of tissue injury could be recognized

Rupture of pericapillary granulated cells with release of its granulae is found to be a sensitive test of tissue injury If a preparation should be regarded as acceptable the number of distrupted cells must not exceed 5—10 %. In the aforementioned series with Tetracain + Biogan the amount of disrupted cells was about 25% and in the cases where Epinephrine was used about 75%.

The experimental model which is developed has proven useful for drug tests and seems well suitable for correlation between ciliary activity and microcirculation. Hereby it is possible further to analyze those complexe mechanisms of tissue injury which is taking place in the mucous membranes of the upper respiratory tract.

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INFRARED THERMOGRAPHY IN OTOLARYNGOLOGY

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The infrared emission patterns from the body can be registered and analysed by infrared thermography This method, which has recently been introduced for medical purposes, has proven of value in cases of inflammation, peripheral vascular disease and to some extent in superficial tumours. Its possible use in otolaryngology has been evaluated with respect to diagnosis and follow up of treatment

During recent years attention has been paid to modern technics as a tool for registration of biological events Along this line I wish to relate an attempt that has been made objectively to register the infrared emission from different biologic tissues The results which will be shown in the following should be regarded preliminary because of the small number of patients hitherto analyzed As a matter of fact the variations of emission in normals are not entirely analyzed.

The apparatus used has been developed by AGA, Swedish Co It is schematically illustrated in fig 1 The method has several big advantages, one of which is that the registration takes place at a distance of 3 meters from the patient. The measurements are based on the fact that all bodies with a temperature above zero produce an electromagnetic radiation the range and intensity of which is determined by

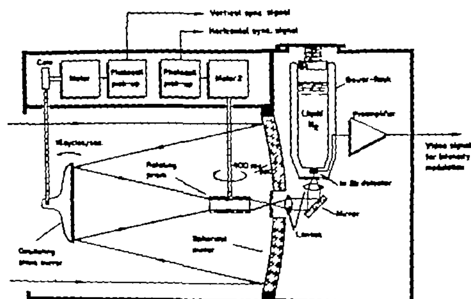


Fig. 1. Schematic sketch showing the principles of AGA Thermovision

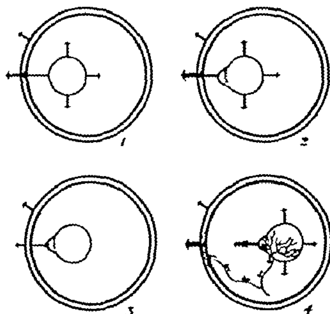


Fig. 2. Schematic outline illustrating those possible w ys in which the surface emission might be modified.

A deeply situated body may increase surface emission 1),
Changes in a deep structure may further increase 2),
or decrease surface emission 3)
A vascular or nervous reflex may change IR-emission in segmental skin area 4).



Fig. 3. Thermogram showing increased emission from ethmoid and frontal sinuses in patient ith a clinical pictur of sinusitis

the absolute temperature of the body It is important to stress the difference between IR-photography and IR-thermography In the former the body is subjected to an IR radiation and the reflected waves are photographically registered on photosensitive plates.

By means of thermography we get a map of dark and light spots on an oscilloscope indicating differences in surface temperatures down to 0 1°C. From biologic point of view it is worthwhile calculating what we are really measuring (fig. 2).

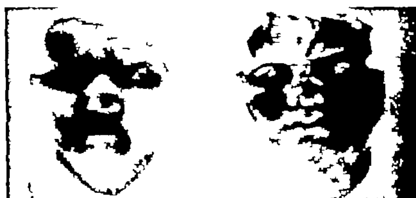


Fig. 1.) Thermogram with left sided Bells palsy
b) Same pati nt after tw weeks treatment with isoxysuprenaline. Note equal emission from both halves of the face aft r treatment.

After analyzing about 500 patients within different kinds of medical branches following applications have proven most useful

1) Different kinds of inflammation
2) Peripheral circulatory disturbances
3) Thermal injuries
4) Tumours

The resolving power with this apparatus is about 2—4 mm but a modified complement with a resolving power of down to 10 μ is under construction.

Until now made work indicates that this method might be a valuable complement to clinical diagnostics and follow-up studies. Further studies with this method will show its usefulness within otolaryngology

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RESPIRATORY MECHANICS IN NORMAL CHILDREN AND IN CHILDREN WITH PSEUDOCROUP [1]

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The lung resistance (including the resistance of the upper airway) was studied with special technique in healthy children and in children with subglottic laryngitis. Th effect f d namic compression was discussed as n explanation of the inspiratory distress.

The aim of this investigations is to study mechanical factors affecting the airway resistance in children with pseudocroup (subglottic laryngitis).

Methods

Lung resistance, Rl, was measured with the method described by Allander Ingelstedt, Jonson and Westling (1964) and later modified by Ingelstedt and Jonson (to be published) The method is based on recording of the esophageal pressure according to Milic Emili, Mead, Turner and Glauser (1964) while the subject is breathing through a volume flow regulator (VFR). A volume flow regulator is a valve admitting a known, constant volume flow regardless of the effort of the subject. The air flow is interrupted several times during each breath with a solenoid operated shutter During the interruptions the esophageal pressure equals the static pressure component, and a graphic procedure allows the resistive pressure component, (Pres), to be determined during flow The resistance was calculated as far as possible at 50 % vital capacity according to the formula. $Rl = \frac{Pres}{\dot{V}}$

During inspiration the gas pressure at a point in the airways amounts to atmospheric minus the flow resistive pressure drop and the accelerative pressure drop from the airway opening down to that point. The pressure outside the extrathoracic airways equals the atmospheric. Thus a net pressure tending to compress the extra thoracic airways exists during inspiration. (For details see Ingelstedt and Jonson 1967). This phenomenon is called dynamic compression of the upper airways (dcuaw). If the normal rigidity is lost dynamic compression may cause severe increase in the inspiratory resistance. In studies of dynamic compression of the upper airways the use of VFR offers great advantages, as shown by Ingelstedt and Jonson (1967). With increasing inspiratory effort, recorded as an increased negative pressure in the mouth (Pm) the pressure causing dynamic compression is correspondingly increased without any change in flow rate, and the effect on the resistance is studied.

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[1]) This investigation w supported by grants from th Swedish N tional Association against Heart and Chest Diseases.

The children were carefully made acquainted with the equipment and the investigators. The nasal cavity was anaesthetized by tetracaine 1 solution and the throat by swallowing a spoonful of Xylocaine® viscous (Astra). Finally the introduction of the esophageal balloon offered little or no anxiety or discomfort. This was a pre-requisite for performing the investigation, since the intelligent and positive co-operation of the child was necessary.

No data of the lung resistance in the height and age-groups expected to get pseudocroup can be found in the literature. Therefore a small group consisting of 8 healthy children (aged 3—8) was investigated.

Results

Data of lung resistance at 0.25 or 0.5 LPS did not show any difference in subjects. Figure 1 shows the inspiratory resistance in the different subjects as the mean values and the ranges of the single observations. As expected the smaller the child the higher the resistance. The range of the single observations was also large in small children. This may partly be explained by difficulties in performing the manoeuvre for determination of the vital capacity necessary to ensure that data are obtained at 50 % vital capacity.

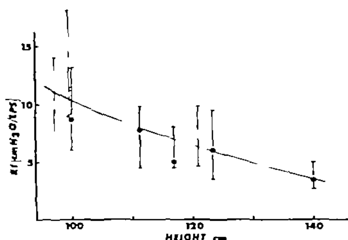


Figure 1. Mean values and ranges of RI in the individual normal children. Line is drawn according to best visual fit.

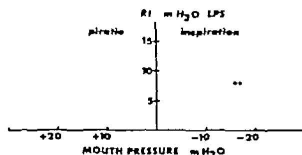


Fig. ... piratory and ... piratory RI as ... nction of mouthpiece pressure ... of ... and ... inspi... recent history of pseudocroup. The normal children show the same pattern

It could be suspected that inspiratory resistance in children, even normal ones, with their relatively soft and narrow airways, might be influenced by dcuaw Fig 2 shows the resistance at a flow rate of 0.25 LPS and a mouthpiece pressure varying from +28 to −23 cm H_2O No evidence of dcuaw could be seen The same was true of all normal subjects. Nor could any other systematic difference between expiratory and inspiratory resistance be noted (*Table 1*)

TABLE 1

	Sex	Age	Height (cm)	Weight (kg)	Mean Ri insp. (cm H_2O/LPS)	Mean Ri exp. (cm H_2O LPS)
Normal	♂	4 1/4	97	15	9,1	9,4
	♂	3 1/2	100	18	8,4	9,5
	♀	4	100	18	13 7	11 0
	♀	5 1/3	111	19	7	7,9
	♂	5 1/2	117	18,5	5,0	5,8
	♀	8	121	20,5	7,5	7,8
	♀	7	123,5	20,5	6 0	6,2
	♂	8 1/4	140	41	2,9	3,3
Status post pseudocroup	♂	3	100,5	16,8	6 0	8,6
	♂	3 1/2	100,8	1[illegible],5	18,0	16,2
	♀	4	105	16,5	9,5	10 0
	♀	4	105	18,5	8,8	8,5
	♂	4 1/4	106	16,5	10 1	9,8
	♀	5 1/2	10[illegible]	1[illegible],5	4,4	5,9
	♀	6	110	19	9 0	10,2
	♂	4 1/4	112	23,5	4	3,8
	♀	6 2/3	119	20	7,8	6 6
Pseudocroup Acut attack	♂	7 1/2	140,5	21	1,9	14 0

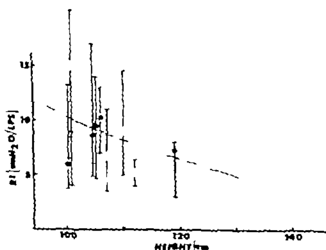


Figure 3 Mean values and ranges of Ri in the individual subjects with recent history of pseudocroup The broken line is derived from the data of the normal children, fig. 1.

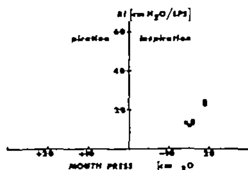


Figure 4. Inspiratory and expiratory Rl as a function of mouthpiece pressure illustrating the dcuaw in a child with acute pseudocroup attack.

A group of nine patients (aged 3—6) were examined 30 minutes to 2 days after an attack of pseudocroup.

Fig. 3 shows that there was no systematic difference in these children compared to the normal ones. Nor was there any sign of dcuaw in any of them. The inspiratory and expiratory Rl were equal in the individual child.

It has until now been possible to examine one child only during an attack of pseudocroup. The resistance in this child (age 7 1/2, height 140.5 cm) varied from 6 to 60 cm H_2O/LPS (fig. 4). The resistance was higher during inspiration than during expiration. The resistance was highest at highly negative mouth pressures which is attributed to dcuaw.

Discussion

The resistance values in the normal children were slightly higher than data from four normal children (height 109—134 cm) reported by Briscoe and DuBois (1958). This may be attributed to random error or to the differences in methods. The method of Briscoe and DuBois does not include lung tissue viscous resistance. Our data however seem to be considerably lower than those (height > 124 cm) reported by Engström, Karlberg and Swarts (1962). This may again, at least to some extent, be explained by differences in methods, as the method used by them does not correct for hysteresis in the static pressure-volume behaviour of the lung.

No effect of dcuaw could be demonstrated in the normal children nor in children with a recent history of pseudocroup. Thus the severe inspiratory distress in children with pseudocroup does not seem to be attributable to loss of rigidity of the support of their extrathoracic airways. In the child with an acute attack there was a great increase in Rl both during expiration and during inspiration. This can probably be attributed to a severe subglottic oedema. With severe stenosis in the extrathoracic airways evidence of dcuaw may be expected as was in fact the case in this child. Most attacks of respiratory distress in children with subglottic laryngitis develop some time after the child has fallen asleep. It is possible that the oedema is favoured in the recumbent position by the increased venous pressure. The resistance in nose, mouth and glottis may increase in the recumbent position and during sleep for the same reason and because of a possibly impaired nervous control.

As the degree of dcuaw is related to the resistance of the airway from the compressed point to airway opening dcuaw and a dyspnoic attack may be the result.

Jackson and Jackson (1959) proposed a glottic valve mechanism as an explanation of the inspiratory obstruction in cases with laryngeal dyspnea. This conception was called in question by Carlens (1960). Nor have we found anything to support this theory

The mechanisms leading dyspnoic attacks in children with subglottic laryngitis are still to be investigated. It is likely that the subglottic oedema and a concomitant dcuaw play a great role in the attacks. The dcuaw may be eliminated by even a slight positive pressure in the mouth overcoming the resistance above the compressible segment. This agrees with the clinical experience that it is easy to ventilate a child with subglottic laryngitis that has stopped breathing, for example by mouth-to-mouth technique.

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SIGNIFICANCE OF ENDOLYMPHATIC SECRETION TO THE FUNCTION OF THE HAIRCELLS

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Toront Canada

Cholinergic and drenergic inhibitors and stimulants ha been topically applied t preparations of the labyrinth in cold blooded animals. This showed that a cholinergic mediator conveyed the haircell stimulation t the nerve endings of the vestibular nerve. The possible source of this mediator in the secretory epithelium f planum semilunat m and the possibilities of its action on the haircells a d nerve endings are discussed.

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CANADA

THE ULTRASTRUCTURE OF THE SPIRAL GANGLION IN THE GUINEA PIG

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The spiral ganglion of the guinea pig is composed of uniform bipolar nerve cell bodies, surrounded by sheaths of compact myelin completed with layers of loose myelin.

The perikarya are densely packed with organelles, especially endoplasmic reticulum, well developed Golgi-zones, mitochondria and osmiophile bodies.

A little group of hitherto not described nerve cell differ significantly from the main part of cells in having no myelin sheath but only one single layer of Schwann cell cytoplasma, little endoplasmic reticulum but many neurofilaments. They have a big nucleolus and their axons are very thin without a sheath of compact myelin. Preliminary experiments of strong white noise stimulation do not show significant alteration in the amount of RNA granules in the perikaryon. There seem to be an increasing number of so-called nuclear caps consisting of several layers of endoplasmic reticulum arranged concentric with the nuclear membrane.

The spiral ganglion is anatomically and functionally closely related to the cochlear duct. With different influences on the inner ear physiological as well as toxic, the question is often raised whether the nervous apparatus is altered. It must therefore be of interest to know the fine structure of the spiral ganglion under different conditions. Up to now the electron microscopical investigations of the inner ear have been concentrated mainly on the cochlear duct.

In a series of publications, Rosenbluth has worked with the peripherial ganglia of the eighth cranial nerve of goldfish and rat, based on an interest in the structure of the myelin sheath and in these works gave a description of these cells.

To otologists the most interesting observation made, was, I believe, that he could distinguish 2 types of spiral ganglion cells in the rat, one type being densely packed with granular endoplasmic reticulum and few neurofilaments and a myelin sheath consisting of several »loose» Schwann cell layers, and another type with a small quantity of endoplasmic reticulum, many neurofilaments and neurotubuli, and a compact myelin sheath. Our investigations of the spiral ganglion of the guinea pig show that this observation is not in general evident.

Preparations of ganglion cells for electron microscopy were always performed by intravital perfusion in part directly with osmium tetroxide a. m. Palay in part

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with formalin prefixation after the method of Holt and Hicks, or with glutar aldehyde (2 %). The material consisted of 36 animals with an average weight of 200 grammes. The spiral ganglion cell is, like the vestibular ganglion cell bipolar with a somewhat eccentric origin of the two axons. They are rather unique as they are surrounded with a compact myelin sheath. In lower animals myelin covered nerve cells occur more often. The cells make a spiral shaped heap and seem to be connected loosely with one another therefore by aldehyde fixation, where shrinking is unavoidable extracellular spaces are seen very clearly. This artefact can almost be eliminated by direct perfusion with osmium. There is practically no collagen between the cells. In addition to axons, capillaries are seen to be situated so that the distance to the remotest cell is two — three cell diameters.

The spiral ganglion cell is 22—28 microns long and 12—16 microns broad and regular ovoid. Contrary to the observations made by others we have not observed any differences in the size in the various turns.

The structure of the myelin sheath which is made of one — two Schwann cells differs clearly from that of the axonal myelin. Towards perikaryon three — six layers of so-called loose myelin with a significant content of cytoplasmic organelles, mitochondria, vesicles, and the likes are seen. These layers then become a four to eight layered compact myelin with the typical structure of major dense lines consisting of the merged inner layers of the triple layered cell membrane of the Schwann cell. Outside the compact myelin there are still more layers of loose myelin and the perikaryon of the Schwann cell which contain the usual organelles. The mitochondria are compared with the mitochondria of the nerve cell, big and dense with densely packed cristae and dense matrix. The more irregular structure of the myelin of the ganglion cell is comprehensible when considering the development of the myelin (the wrapping theory). The myelin is formed partly by the Schwann cell's spiral movement in relation to the nerve cell, partly by a sheet shaped growth following the growth of the neurone. To make a comparison, it will always be easier to wrap a cylindric bottle than a Chianti bottle.

The axonal myelin in the afferent nerves consists of 20—30 layers of regular compact myelin. Normally no Ranvier's nodes are to be found on the cell itself. The first node on either side, lies at a distance of about 1 cell length from perikaryon. Due to the difference in the development of the myelin it acquires an asymmetrical structure. However Schmidt Lantermanns clefts are often found in the myelin of the cell.

In the perikaryon of the nerve cell lie densely packed organelles and one can find a very well developed network of rough endoplasmic reticulum, the cisterns of which often are arranged parallel but most often lie in quite irregular groups, making up Nissl-bodies as known from light microscopy. In between the cisterns the cell matrix frequently is a little more dense and contains many ribosomes. The endoplasmic reticulum is apparently situated randomely in the cell apart from axon hillocks which is characterized exactly by its lack of Nissl substance. No sharp demarcation is to be observed, as when using the light microscope.

The Golgi complex is extremely extensive and widely distributed often in the well known cup-shaped arrangement made up of flat cisterns which often are

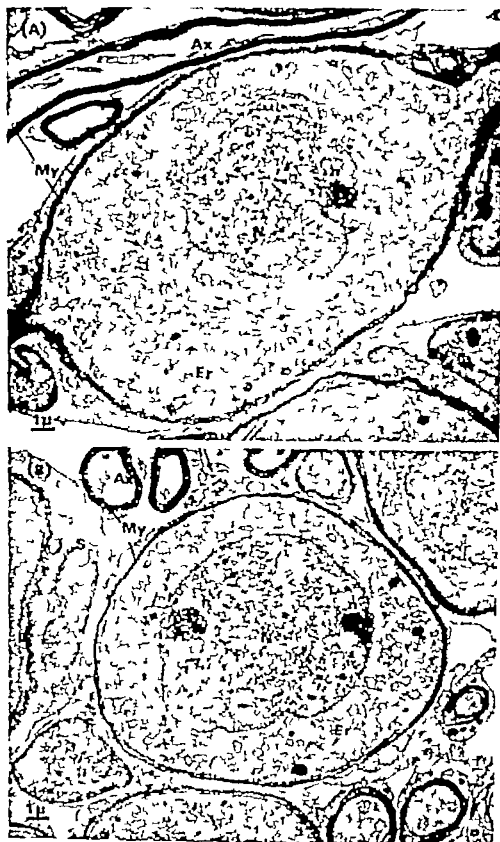


Fig. 1 (A) Longitudinal section of spiral ganglion cell. (My: myelin sheath, N: nucleus, n: nucleolus, Er: endoplasmic reticulum, S: Schwann cell, Ax: Axon) (B) Transversal section of spiral ganglion cell. Note the unmyelinated nerve fibe with Schwann cell cytoplasma spiraling around the fiber (arrow). (Osmium perfusion, Uranylacetat staining, × 5 200)

empty with dilatation of the edges. Situated very closely around the cisterns several vesicles are seen in a dense matrix, some of these vesicles contain a dense core, others a radiate coating. Spread in the cytoplasma »dense bodies« of the usual lysosomal type are found. Multivesicular bodies are distributed in the perikaryon as well as in the axon, often surrounded by smaller vesicles.

In glutaraldehyde fixed specimens perikaryon microtubules and neurofilaments are seen everywhere. The concentration of these is increased towards the emission of the axons.

The central axon which runs out from »axon hillock« is normally twice as thick as the peripherial axon, three — five microns, and acquires immediately the content of organelles characteristic for axons, whereas the peripherial axon goes over uniformly into the perikaryon. On the whole, the nucleus is regularly round but the triple layered nuclear membrane is very often twisted making so-called »nuclear rods« i.e. cytoplasmic infoldings, which are rich in ribosomes. In the nuclear membranes there are nuclear pores with varying distances, closest where the nucleolus is apposed to the membrane or in the »nuclear rods«.

In these preparations the nuclear plasma is granular. One can distinguish different groups of granules in the sizes of 50—100—150 and up to 300 Å, around the latter is a clear zone.

Nucleolus is often double or triple. Morphologically it is composed of several distinct constituents. The main part is made of a meshwork like heap of dense granular material. In the meshes a less dense granular matrix is found. Clumps of more distinct granules, corresponding to the nucleolus associated chromatin of the light microscopy is superimposed on the nucleolus.

The nucleolus is often situated at the nuclear membrane. Opposite the nuclear pores one may see an empty zone in the nucleolus associated chromatin but the ribosomes accumulate in the perikaryon near the nucleolus. In this area with granular endoplasmic cisterns can also be observed situated concentrically with the cell membrane. However real nuclear caps consisting of many layers [illegible] plasmic reticulum may be found diametrically opposite the nucleolus.

Among the ganglion cells a small quantity of nerve cells (2—4 %) are [illegible] and which in several respects differ significantly from the main group. They are [illegible] placed along the outer border of the spiral ganglion, but can be seen [illegible]. The most predominant characteristic is their lack of a proper myelin sheath as [illegible] are covered only with a single layer of Schwann cell cytoplasma [illegible] Schwann cells. These nerve cells are small and perikaryon is less [illegible] smaller amount of endoplasmic reticulum and less mitochondria [illegible]

Fig. 2 (A) Axon hillock. Note the concentration of neurofilaments and [illegible] of the ganglion cell. The myelin sheath has the typical structure for cell [illegible] Uranyl staining, × 333 00) (B) Unmyelinated nerve cell. The nucleolus [illegible] by the external formation of nucleolus associated chromatin. (O[illegible] (C and D) Details from perikaryon from myelinated and unmyelinated [illegible] mentioned there is accumulation of neurofilaments and microtubules [illegible] mitochondria and cisterns of endoplasmic reticulum. (S: Schwann [illegible] [illegible] Uranyl acetat [illegible] × 335[illegible]

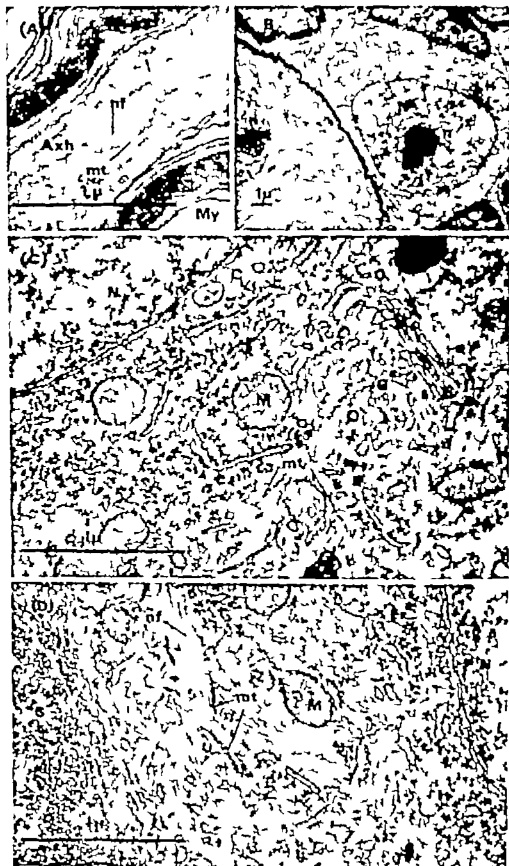

(A)
Axh
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B
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Go
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Fig. 3. (A) Details from perikaryon of ganglion cells from white noise treated animal (127 db 13 hours). Nuclear cap consisting of several layers of endoplasmic reticulum arranged concentric with the nuclear membrane (nm) (np: nuclear pores, Mvb: multivesicular body, G: Golgi zone, M: mitochondrion). (Formalin perfusion, Uranyl staining, × 42000). (B) Nucleolus — nuclear membrane relations. Note the infoldings of the membrane around the nucleolus, the nuclear rod (nr) and the clear zones in the chromatin inside the nuclear pores. (Formalin perfusion, Uranyl

packed with neurofilaments and microtubules. The nucleolus is often large due to a remarkable aggregate of nucleolus associated chromatin. Normally they deliver one — two unmyelinated axons the diameter of which is less than one fifth of the myelinated axons. Possibly they are myelinated at some distance from the perikaryon. At any rate some of these cells deliver a myelinated axon beginning with a half node directly on the cell. There is no doubt that many of the unmyelinated nerveaxons, which are seen in the spiral ganglion originate from such cells. Their function is unknown. It might be proneurones which have never fully developed. Another possibility is that they might have a special task. Up to now we have not been able to follow the course of their axons.

We have started experiments with noise stimulation in connection with previous cytochemical investigations of the basophilia of the spiral ganglion cell (Pakkenberg and Thomsen). Five animals were given White noise 227 db for four hours, one animal for 13 hours. No conspicuous change in the amount of ribosomes could be observed in the electron microscope. The light microscopical observations of the rearrangement of the endoplasmic reticulum can, however, be confirmed as there seems to be a tendency in a larger number of cells that the cisterns are arranged concentrically with the cell membrane in one to eight layers than is the case in non treated animals. Any deleterious effects of the noise stimulation could not be observed.

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ON GLYCOGEN IN THE COCHLEAR DUCT OF FOETUSES AND YOUNG OF ALBINO RATS

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The presence of glycogen in the cochlear duct was followed through various stages of the embryologic development of the rat and in infantile rats from the 1st day after birth till the ear had attained its full function l maturity. The investigations revealed a changing glycogen pattern in the cochlea throughout the development of the ear. When the organ of hearing had attained functional maturity the glycogen pattern was as in adult animals.

GLYCEROL TEST IN MÉNIÈRE'S DISEASE

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Ingestion of glycerol, 1.5 g/kg body weight causes a transient reduction of th hear ing loss in th early tage of Ménière disease I dvanced Ménière cases with mainly flat loss th glycerol ffect is less regula I some cases improvement occur the threshold shifts being most pronounced in the consonant area and associated with considerable speech discrimination ga n. No glycerol ffect is see in normals or cases of cochlear deafness of other types. The action f glycerol is purely osmotic and the ffect in Ménière cases is probably due to reduction f intralabyrinthine pressure. Th findings indicat that endolymphatic hydrops contri b tes t th hearing los in Ménière' disease on mechanical basis by hydrodynamic damping of the organ f Corti. In clinical practice positive glycerol test indicates reversibility and that treatment with d uretic drugs may be f alue

Though the cause of Ménière s disease is still obscure it is known that one component of the pathologic mechanism is endolymphatic hydrops. Histologic evidence of distension of the endolymphatic system has been found so far in 2 cases, most of whom had reached an advanced stage of the disease (cf Altman & Kornfeldt, 1966). The underlying cause may be of biochemical nature (see e.g Schuknecht 1963)

It is uncertain to what extent the symptoms, i.e. hearing loss tinnitus and vertigo are due to the hydrops or to the underlying cause. The effect of glycerol ingestion (Klockhoff and Lindblom, 1966) indicates that the cochlear symptoms are partially due to hydrops, probably through hydrodynamic damping of the organ of Corti.

Glycerol is given perorally as a single dose of 1.5 g/kg body weight on a fasting stomach The effect on the hearing loss is examined by repeated tone audiometry and in some cases also by speech audiometry Glycerol produces a transient hyperosmosis in the blood and is thought to lower the intralabyrinthine pressure

In cases of Ménière s disease in the fluctuating stage during bouts of mainly a low-frequency loss, a temporary improvement in the hearing is obtained that reaches a maximum 2 or 3 hours after the intake of the glycerol. A representative case in figure 1 shows that the hearing gain is greatest in the region of the inter mediate frequencies.

Particularly interesting and informative is the effect of a glycerol test in certain cases of mainly flat loss, where a diagnosis of Ménière s disease is suspected but uncertain, and in advanced M nière cases where there is doubt as to whether the irre ersible stage has been reached. An example is given in figure 2. In this case comparative speech audiometry showed a simultaneous gain in discrimination of almost 30 per cent. The patient, a 51-year old man, had had M nière s disease

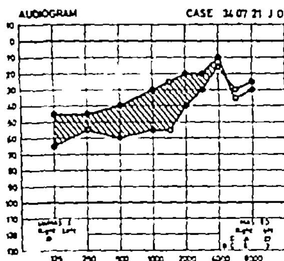


Fig. 1. Hearing threshold improvement 2 hours after ingestion of glycerol 1.5 g/kg body weight in unilateral case of Ménière's disease.

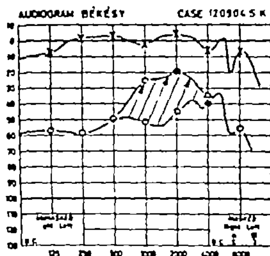


Fig. 2. Hearing gain 3 hours after intake of glycerol 1. g/kg body weight in advanced unilateral Ménière case. Concomitant improvement of speech discrimination ability from 60% at the 70 dB level to ...% at the 55 dB level.

with the full triad of symptoms for 10 years. He now complained of intolerable vertigo with 2 or 3 attacks a week since 1 months. For 6 months he had not noticed any definite spontaneous fluctuation in the hearing. It was considered that the irreversible stage of Ménière's disease had been reached. Surgical intervention with section of the vestibular nerve was considered. However, since the glycerol test indicated that there was some measure of reversibility, the patient was instead given a peroral diuretic (Lasix® 40 mg, twice daily) according to our recent study in which prolonged supply of a diuretic was found to have a beneficial effect on both vertigo and hearing loss (Klockhoff and Lindblom, 1967). On

examination two weeks after the treatment was introduced there was an improvement in the hearing similar to that obtained temporarily with the glycerol test The vertigo disappeared and a previously annoying tinnitus was now barely perceived. At the last follow-up 4 months after the treatment was begun this general improvement was still maintained in all respects. No disturbing side effect were seen. The surgical measures were postponed and it is possible that they will prove unnecessary

Further studies are being made of the effect of reducing endolymphatic hydrops by osmotic dehydration with glycerol and by simultaneous or successive diuretic dehydration with oral diuretics. This is done on variants of M'nière s disease and on other types of inner ear dysfunctions. The aim is to elucidate further the mechanism behind various cochlea-vestibulopathies. The clinical value of the glycerol test as a diagnostic tool and as a guide to diuretic therapy is also examined

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DISCUSSION

G. Herberts I should like to ask D Klockhoff if any change occurred in possible vertiginous symptoms and if the results of vestibular examination changed in any way in connection with the glycerol tests.

I Klockhoff In reply t Prof. Herberts I wish t stat that vertigo has appeared only in few exceptional cases in the rebound phase of the 60 cases of acut hearing improvement w have yet seen induced by glycerol, inspit of the fact that vertigo was mostly the dominating handicap factor Thus our present believe is that vertigo is not directly influenced by the degree of intralabyrinthine hydrops but may rather be due t changes in the unknown, possibly biochemical disturbance However in order t study this question further comparativ vestibular testing has recently been added t the hearing tests.

MECHANISMS OF THE GAS EXCHANGE IN THE NORMAL MIDDLE EAR[1]

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The spontaneous rat of the middle ear ventilation through the E tachian t in the aural flow direction was determined on 2 normal bject for some hour a pres ure flow technique This rat of v tilation was considered to reflect the mal rat of ga volume absorption f om the middle ar pace t th l lood. A sum that the rat of ventilation determined i valid for 24 hours, th daily ventila through th Eustachian tube into the mid lle ea for obt ining normal ea pres conditions only reaches 1—2 ml.

Finally tw accessory mecha i ms re discu sed which m y facil t t the ventila of t e middle ear

The middle ear cavity represents a non ventilated type of gas pocket (I van Liew 19) intermittently open to the atmosphere via the Eustach From this cavity O_2 and N_2 are continuou ly absorbed but CO_2 i in eq with the blood as long as the Eustachian tube functions normally T operates as a pres ure regulator f r the mi ldle ear cavity by now and the in small air portions, which normally replace the volumes of gas absorb the rate of volume absorption of gas from the middle ear cavity sh determined indirectly provided that the air volume flow through t (ΔV_t) needed for obtaining normal ear pressure conditions could be n The primary aim of the present investigation was to determine the nor of ΔV_t in the aural direction as an expres ion of the actual rate of the ga absorption from the closed ear space to the bl od Such information wil further basic knowledges about the middle ear function

The middle ear system comprises a group of interacting parts i e the of the middle ear the ear drum system and the Eu tachian tube A qua description of the mechanisms taking part in the gas exchange is very Several variables must be determined for a reliable measuring of ΔV_t The volume of the middle ar air space V_m the pressure changes in th ear cavity Π_m, and finally the degree of ear drum mobility measured a displacement ΔV_{tm} which i a function of Π_m

METHODS

A D termination of V_m and Π_m (Figure)

A direct communication with the air filled ear space wa produced by pu the ma toid process. The needle was airtightly connected to an electronic system provided with a micropipet filled with water When a known vo

[1] This research was pported b th Swedish Medic l Research Council

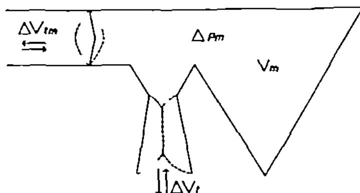


Fig. 1. Variables t be determined i the middle ear system.

V_m: volume f ear pace ΔP_m: pressure changes within the ear space
ΔV_{tm}: lume displacement of the t mpanic membrane ΔV_t: rate f t bal ventilation.

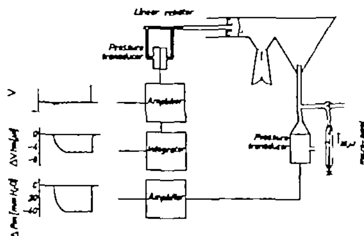


Fig. 2. Diagram of the ear canal flow and the middle ear pressure meter systems.

water was emptied from the pipet a known volume increase occurred within the closed ear-manometer and the resulting pressure change within the system was recorded. V_m was calculated with the aid of Boyle's law (Flisberg, Ingelstedt, Örtegren 1963). At this point, however, two physiologic errors were introduced which could reduce the reliability of this V_m-technique used. Both factors are analyzed under B. They must be analyzed because both of them contribute to an uncontrolled overestimation of the gas volume increase as read from the pipet. Every underpressure applied withing the closed middle ear system will increase the blood content within the vascular network of the mucosa and simultaneously the tympanic membrane is sucked inwards.

ΔP_m was recorded continuously during several hours via the puncture needle in free air-contact with the air-filled ear space.

B. Determination of ΔV_{tm} (Figure 1)

Ear drum movements caused by ΔP_m produced an air flow in the external ear canal.

A catheter was airtightly connected selectively to the bony part of the canal. The free end of the catheter was connected to flow meter. This consists of a specially constructed linear flow resistor in which the pressure drop is a linear function of the air flow. A movement of the ear drum could then be recorded as a simultaneous instantaneous air flow in the auditory canal. With the aid of a special integrator these flow signals were integrated with respect to time giving ΔV_{tm} which was directly recorded. The advantage of using a flow detection technique is that the mobility of the ear drum is never restricted by any significant counterpressure in the auditory canal. Sensitivity: a volume displacement of the tympanic membrane of 1.0 microliter can be measured with an error of ± 5 %. Linear frequency response 100 % 0–8 cps. This method will be published in detail (Ingelstedt, Ivarsson and Jonson).

When determining V_m the actual ΔV_{tm} caused by the aural underpressure must be recorded simultaneously with ΔP_m. The volume increase as to be read from the pipet is corrected by ΔV_{tm}.

In order to obtain a correct calculation of V_m it is further important to find out if application of a moderate underpressure to the middle ear cavity will produce any serious increase of the blood content in the middle ear mucosa. This factor was elucidated in the following way. By using a special venous catheterization technique (Lindell, Nilsson, Roos and Westling 1962) a catheter was inserted into a cubital vein and was advanced to the internal jugular vein under fluoroscopic control until the catheter tip reached the foramen jugulare. The catheter was connected to an electromanometer. Then after incision of the tympanic membrane the flow meter was connected to the ear. Now the intra-aural volume changes ΔV_m, representing changes in the blood volume in the mucosa, were studied as a function of the intravenous pressure changes close to the ear. Such studies were performed either by changing the posture from a recumbent to a sitting position or by compression of the veins on the neck. The results obtained showed that a moderate increase of the intravenous pressure of the same order as the underpressure applied to the middle cavity for the routine determinations of V_m only produced a moderate capillary venous stasis within the aural mucosa. The error introduced by the vascular factor in the V_m technique could then be estimated from the ΔV_m recordings: 1–3.8 %. This part of the investigation will be published in detail (Ingelstedt, Ivarsson and Jonson).

Investigation and experimental performances

After the application of the puncture needle to the air cells and of the flow meter to the auditory canal the subjects were sitting comfortably in a chair for several hours. No instructions were given and all spontaneous pressure-flow changes were continuously recorded. We had not expected to register the very slowly developing intra-aural underpressure and the simultaneous slow movement of the tympanic membrane inwards as isolated effects of a gas volume absorption

from the closed middle ear to the blood. It proved possible however to record the rapid events in the closed system as rapid and defined pressure-flow changes at every pressure equilibration moment when the Eustachian tube opened.

For minimizing the drift by temperature sensitivity of the transducers all experiments were performed in a specially constructed climate room at a constant temperature. Every change in the atmospheric pressure was observed.

At the end of each experiment V_m and the static compliance of the ear drum system were determined. This latter determination was performed in the following way: graded under and overpressure was applied to the middle ear cavity via the puncture needle in the mastoid process. Simultaneously the resulting degree of volume displacement of the tympanic membrane was recorded.

RESULTS

In Fig 3 the rate of the gas exchange during a period of 50 minutes in a normal middle ear is illustrated. At the top of the figure appear recordings of ΔV_{tm} expressed in microliter followed by ΔP_m beneath, expressed in mm H_2O. As appears from the figure an underpressure is slowly built up in the closed system sucking the tympanic membrane slightly inwards. Now and then this course is broken during the deglutitions. The Eustachian tube opens and small gas portions are sucked into the ear cavity the tympanic membrane pulls outwards its neutral position by its elastic recoil and the underpressure is equilibrated.

ΔV_t at every deglutition was calculated from ΔV_{tm} ΔP_m and V_m with the aid of Boyle's law

$$V_m \cdot P_m = (V_m - \Delta V_t + \Delta V_{tm}) \cdot (P_m + \Delta P_m)$$

Clearing and solving for ΔV_t

$$\Delta V_t = \frac{V_m \cdot \Delta P_m}{P_m} + \Delta V_{tm}$$

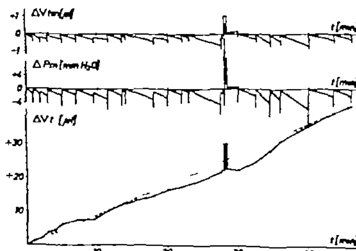


Fig. 3. The rate of tubal ventilation (ΔV_t) calculated from the actual V_m (8,31), ΔP_m and ΔV_{tm} determined on normal middle ear

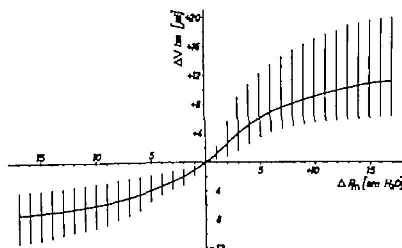


Fig. 4 The static pressure volume relationship of the ear drum system determined on 9 normal ear cases.

P_m equals atmospheric pressure minus the pressure of saturated water vapor at 37°C, since water vapor is regarded as non-compressible. The ΔV_t values are in the bottom of the figure added at every moment of deglutition The resulting slope reflects the gas volume absorption from the middle ear to the blood.

At the 28-minute point the subject is yawning This phenomenon will be discussed beneath

In Fig 4 the static compliance of the ear drum system is given when ΔV_{tm} is recorded as a function of ΔP_m In the upper right quadrant is seen the degree of drum volume displacement outwards produced by various amounts of over pressure in the middle ear In the lower left quadrant the corresponding degree of volume displacement inwards by underpressure. The mean curve and the range of all the different volume displacement values recorded from nine normal middle ear cases are presented. It appears that at overpressure from 15 to 17 cm H_2O the volume displacement varied from 6 to 20 microliter while at the same amount of underpressure only a volume displacement from 4 to 10 microliter was obtained These figures are somewhat smaller than those earlier reported (Flisberg Ingelstedt and Örtegren 1963) This difference is mainly due to the fact that we now use a better technique for the ΔV_{tm}-determinations.

Once or twice every hour during all experiments on normal subjects we regularly recorded spontaneously appearing rapid and strong inward movements of the tympanic membrane (ΔV_{tm}) after which the drum moved back again. Such situations are illustrated in Fig 5 On the tracings to the left and in the middle of the figure ΔV_{tm} and ΔP_m are recorded simultaneously correspondingly the ΔV_t values are calculated at the bottom. It appears from both situations that the ear drum is actively pulled inwards because the drum movement simultaneously produces an overpressure in the middle ear space During this period the Eustachian tube opens and some gas is pushed out from the middle ear through the tube as appears from the ΔP_m recordings. To the right in the figure the same phenom-

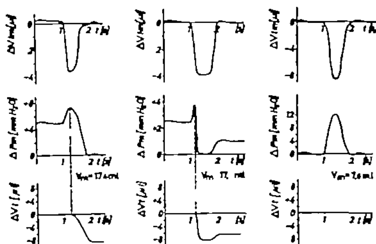


Fig. 5. Ear drum movements and intra-aural pressure changes induced by contractions of the tensor tympani muscle. On the tracings t th left and in the middl f the figure the t be opens during tensor contractions, t the right the t be remains closed.

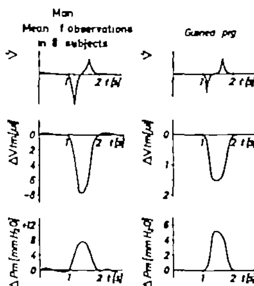


Fig. 6. T the left
mean curves from 8 subjects of the rat of air flow in the auditory canal ( ), of the ear drum ol me displacement (ΔV_{tm}) and the resulting intra-a ral pressure hange (ΔP_m) t men ear pace olume (V_m) of 10 ml.
T th right
corresponding curves obtained from 5 guinea-pigs. Mea of th V_m 3 ml.

enon is illustrated, but now the tube does not open. To the left in Figure 6 a mean curve is constructed from recordings of this event obtained in 8 subjects. Th mean volume displacement of the drum was 7.6 microliter (range 6 8 mi liter). The resulting mean pressure curve within the ear is shown bel w

The subjects were regularily asked if they had felt anything particular in connection with these ear episodes. Sometimes they told us about belchings, which then occurred simultaneously with the recorded middle ear changes, but many times they had not felt anything at all. Similar middle ear effects could be induced by belchings after drinking sodawater but now the drum displacement was regularily smaller than those appearing spontaneously. Small but similar effects could also be recorded during voluntary contractions of the soft palate and of the base of the tongue during voluntary eye closure or when an air jet was blown against the eyes. All these findings prove that we are registering ear drum effects caused by contractions in the tensor tympani muscle.

In experiments on the guinea-pig Handl (1956) demonstrated the same type of spontaneous drum movements, which were registered with ear manometry. He could also directly observe the tensor tympani contractions. In figure 6 this phenomenon is recorded on guinea-pigs. We then used our instruments in the same way on the animals as on human subjects. Observe the similarity of the tracings.

During our experiments we had many opportunities to study what happens within the middle ear system during yawnings. This is illustrated in Figure 7. The Eustachian tube usually opens during these manoeuvres. To the left appears tracings from a subject with an underpressure in the middle ear just before the yawning. During this episode the tube first opens and then an overpressure is built up within the middle ear. To the right a mean curve is constructed from

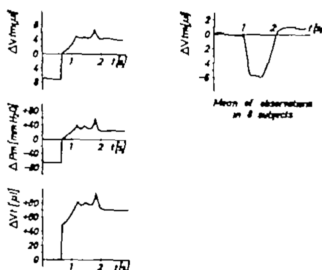


Fig. Middle ear recordings obtained during yawning.
To the left:
an original negative intra-aural pressure is converted to a permanent positive pressure during the act.
To the right:
mean curve of ΔV_{tm} calculated from 8 subjects during yawning. Observe that the ear drum is pushed somewhat outwards to a new position outside its original neutral position.

the different ΔV_{tm} values from 8 subjects recorded during yawnings. All had atmospheric pressure in the middle ear before the procedure. First the ear drum is moved strongly inwards but moves back to a new position outside the original position. The mean volume value for this inwards movements was 5.8 microliter (range 4 1—9.5 microliter) The mean volume displacement value for the registered outward volume gain was 1 1 microliter (range 0 4—1.5 microliter)

DISCUSSION

Gases are continuously absorbed from the closed middle ear space to the blood and the Eustachian tube operates as a pressure regulator by now and then admitting air portions into the ear cavity which normally replace the gas volume absorbed These well-known facts provide a clue as to how the tubal function should be studied in the most physiological way Consequently a method was devised with the aid of which a controlled ear aspiration of airs could be studied after direct application of negative pressure into the middle ear space (Flisberg Ingelstedt, Örtegren 1963). The method was applied to clinical ear cases and the results of such an investigations on a great number of chronic otitis have recently been reported (Flisberg 1966)

In the present investigations we have tried to obtain information about the rate of the tubal ventilation needed for replacing the gas volume absorbed from the middle ear under ordinary conditions. No such ventilatory data have hitherto been available. In 3 subjects like the one illustrated in figure 3 we determined the rate of this ventilation for about an hour Assuming that the rate of ventilation determined is valid for 24 hours, the daily ventilation through the Eustachian tube into the middle ear for obtaining normal ear pressure conditions only reaches 1—2 ml.

The middle ear muscles perform multiple functions, both acoustic and non-acoustic, (Blair Simmons 1964)

However there is still some uncertainty as to the muscles and their function particularly with regard to the tensor tympani muscle.

The contractions of the tympani muscles have been studied by different techniques. Most of the investigators have recorded the changes of the acoustic impedance during such contractions.

(Metz 1946 1952; Jepsen 1953, 1955, Klockhoff 1961 Møller 1961 Terkildsen 1961) The muscular activity has further been demonstrated with the aid of ear manometry connected to the external auditory canal (Terkildsen 1957). Finally electromyography of tympanic muscles have been used on animals (Blair Simmons 1964) and on man (Salomon and Starr 1963 Djupesland 1964) The investigations made by Djupesland were skilfully performed on no less than 48 patients.

The activity of the tympanic muscles has generally been induced by sound stimulation or by an air jet blown against the eyes. But several nonacoustic activities of the tympanic muscles have been revealed on man. The muscles are active for example in connection with general motor activities such as voluntary

eye closure, face and head movements, vocalization, yawning, swallowing coughing and laughing

With the present techniques it was possible to register ear drum movements and the simultaneously resulting pressure changes in the middle ear induced by contractions of the tensor tympani muscle. The largest drum movements were regularly recorded when appearing spontaneously either without any feeling of the ear episodes at all or in connection with spontaneous belchings During these tensor contractions the Eustachian tube either opens simultaneously or remains closed (Figure 5 and 6) It is evident from our investigations that at least now and then during its spontaneous contractions the tensor tympani muscle contributes to the ventilation of the middle ear if it appears synchronously with the opening activity of tubal muscles The overpressure produced in the middle ear by the tensor contraction will aid in pushing away and breaking the mucous membranes, glued together within the isthmus portion. In this way the activity of the tensor tympani muscle may facilitate the opening of the Eustachian tube. Such a mechanism has not earlier been described.

Finally it has been reported in the literature that during yawings the Eustachian tube frequently opens and in electromyographic studies an increased activity in the tympanic muscles has been reported. We also regularily found that the tube opens during these manoeuvres. It was moreover found, however that a positive pressure was regularly built up in the middle ear when the tube closes during yawings (Fig 7). We believe that this is due to the fact that the tube in the initial phase of closure will close its lumen somewhat below the isthmus portion, at which latter point it normally starts the closing during ordinary deglutition. When the final closing occurs during yawnings, however the air within this upper portion is inflated into the closed middle ear

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A CLINICAL EXPERIMENTAL INVESTIGATION OF THE RATE OF CELL PROLIFERATION (RCP) IN HUMAN MALIGNANT TUMOURS

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Oslo

The investigation is based upon mitotic counts in malignant tumours following injection of a mitotic inhibitor The RCP corresponds with the duration of symptoms. Between the clinical growth and the RCP there is however a considerable discrepancy which can only be explained by a very substantial cell loss. This cell loss is discussed.

eye closure face and head movements, vocalization, yawning, swallowing coughing and laughing

With the present techniques it was possible to register ear drum movements and the simultaneously resulting pressure changes in the middle ear induced by contractions of the tensor tympani muscle. The largest drum movements were regularly recorded when appearing spontaneously either without any feeling of the ear episodes at all or in connection with spontaneous belchings. During these tensor contractions the Eustachian tube either opens simultaneously or remains closed (Figure 5 and 6) It is evident from our investigations that at least now and then during its spontaneous contractions the tensor tympani muscle contributes to the ventilation of the middle ear if it appears synchronously with the opening activity of tubal muscles. The overpressure produced in the middle ear by the tensor contraction will aid in pushing away and breaking the mucous membranes, glued together within the isthmus portion In this way the activity of the tensor tympani muscle may facilitate the opening of the Eustachian tube Such a mechanism has not earlier been described.

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a history of preceding head injury should heighten the clinical suspicion of a cranionasal fistula, even though simultaneous CFR may not be demonstrable Pneumocephalus, first demonstrated by Chiari (1881) also indicates the presence of a cranionasal fistula In pneumocephalus, a very rare condition, air is present in the ventricular system or in the brain tissue.

Confusion with allergic rhinitis may occur particularly since both conditions produce an irresistible urge to sneeze which in both cases produces a clear fluid

Radiography of the skull and paranasal sinuses may reveal a fracture. It is also possible that air in the cranial cavity with fluid level in the ventricular system can be demonstrated in these cases of CFR in which pneumocephalus occurs but as pointed out above this is extremely rare. In many cases it may be extremely difficult to detect by radiography a fracture in the posterior wall of the frontal sinus, since the bone structure is very thin. Opacity of the frontal sinus or detection of a thick mucous membrane may often be the only signs of a fracture with cranionasal fistula.

Usually the patient does not lose the sense of smell on the side of the fistula but if the original head trauma has been severe this may occur Anosmia may also be present on the basis of the trauma as a contrecoup manifestation of an occipital blow without fracture of the anterior fossa floor and without CFR

Treatment

The operative measures in these chronic cases of CFR have usually been effected via frontal craniotomy approach (Dandy 1926 Cairns 1937 Adson 1941 Gurdjian & Webster 1953, Thomas et al. 1960 and Gotham et al. 1965)

The present author has treated six chronic cases with a cranionasal fistula in the region of the frontal sinus with autogenous osteoplasty of one or both frontal sinuses.

Method

A curved incision is first made from the side of the upper nose along the underside of the eyebrow (fig 1). The incision passes through the periosteum, but care must



Fig 1 The incision.



Fig. 2. The drilled aperture in the front wall of the frontal sinus.



Fig. 3. The lid formed from the iliac crest in position in the drilled aperture

be taken not to damage the branches of the supraorbital nerve. The periosteum is detached from bone surface. An electric drill is used to penetrate the frontal sinus from the lower part of the anterior wall of the sinus. Enough bone to allow good visibility of all the pouches of the frontal sinus is drilled away from the anterior wall (fig. 2). Subsequently the mucous membrane is carefully removed. Small forceps and the drill are used for this purpose. The mucous membrane of the upper part of the nasofrontal duct is also meticulously removed. The fracture is exposed. Should the mucous membrane have grown across the exposed dura it is carefully removed. Bone tissue is taken from the iliac crest, both cortical and spongy substance. A bone plug is first formed, of which one side is composed of cortical bone and the other of spongiosa. This plug is forced into the nasofrontal

duct. It is fitted closely for the spongiosa accommodates itself to the duct. A plate of spongiosa is placed across the dura and the tear after which the whole frontal sinus is closely filled with spongiosa. If some small pouch of the frontal sinus is difficult to fill with spongiosa, adipose tissue, taken from the skin incision over the iliac crest, is inserted. The main filling, however consists of bone tissue. After the whole frontal sinus has been filled with spongiosa, a lid of cortical bone is formed exactly equal in size to the aperture in the anterior wall of the frontal sinus. A piece of cortical bone of a suitable size and curvature is readily obtainable from the iliac crest. If the intersinus septum is not intact a similar osteoplastic operation is performed on the other side through a corresponding incision. The wound is closed layer by layer the periosteum and the subcutis by catgut, and the skin by silk sutures. No drain is used

Postoperatively the patients were treated with antibiotics. They all had uneventful recovery and all symptoms of CFR disappeared. The patients stayed in hospital for about 10 days after the operation. The author will describe in detail the operated cases in another article (Grahne 1967).

Discussion

This method of operation is extracranial and involves certain advantages when compared with the intracranial methods. The operation, carried out under intubation anaesthesia, is a minor intervention. It involves no further damage to the brain which may have been affected by the preceding trauma. The method can naturally only be applied in cases in which the fracture and the cranionasal fistula are in the region of the frontal sinuses. In most cases of chronic traumatic CFR, however the fistula does seem to have been located in this region as was shown by Morely et al. (1957)

In many cases the diagnosis was difficult. Several patients had been treated for recurrent meningitis without tracing the causative factor One patient had received treatment for allergic rhinitis.

There were some cases in which no definite fracture line was detectable by radiography but in all cases a certain opacity was visible in the frontal sinus or sinuses. Tomography of the frontal sinuses was sometimes of some help in the diagnosis.

Postoperatively there was no cerebrospinal fluid leak, and the patients said already after a few days that their head felt better and »different». It is interesting to note that the relationship between secretion and resorption of the cerebrospinal fluid was apparently very soon restored to normal Some patients lost considerable quantities of cerebrospinal fluid before the operation.

Postoperative radiography showed at first a blurring of the contours of the frontal sinus, and cases where several months had passed since the operation, showed a complete ossification of the frontal sinus with a bone structure that did not differ from that of the surrounding frontal bone.

It is of course important, that all mucous membrane be removed from the frontal sinus. The aperture in the anterior wall of the frontal sinus must be large

enough to enable removal of the mucous membrane under visual control. Large pieces of the mucous membrane can often be removed with forceps and the remainder with the drill, which proved to be very effective. It is of great importance that periorbital pouches, if any are opened and all the mucous membrane removed.

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DISCUSSION

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Wouldn t a wide exposure of th frontal sinus(es) by means of an osteoperiosteal flap be suitable in some cases of cerebrospinal rhinorrhea. Such an opening ensures good view and no bone transplantation is required t fill operatively caused defect.

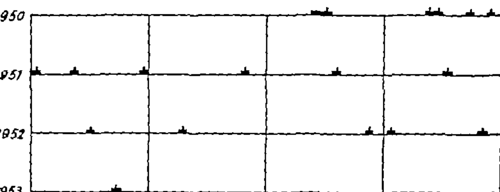
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TREATMENT OF JUVENILE PAPILLOMA OF THE LARYNX WITH RESIN OF PODOPHYLLIN

F. Fabritius, Namsos, Norway

During the last 17 years three cases of juvenile papilloma of the larynx have been treated in ur hospital. The literature on this subject is voluminous, with valuable contributions from inish authors. The therapy suggested varies greatly and new suggestions are still forthoming, the last one being treatment with ultrasound. Reports on the end results of the different ypes of treatment are not encouraging. However careful excison followed by local application f a resin of podofyllinum is a method which has kept its place through many years.

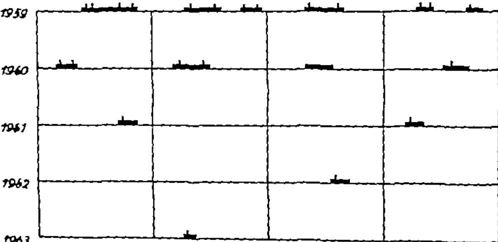
F.A.B. 3years



Control in May 1956 = 16 hospitalizations + 17 treatments

Fig. 1

T.W. 2 years



Control in June 1965 = 14 hospitalizations + 22 treatments

Fig. 2

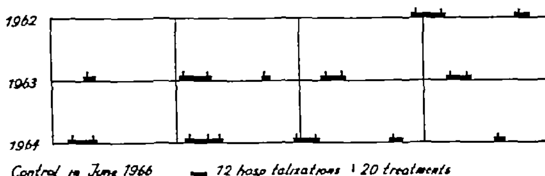


Fig. 3.

Our three patients were treated according to the latter method. The duration of th treatment, th number of hospitalizations and the number of laryngoscopies with excision and application of podofyllinum in the individual case are shown on table 1 The importance of repeated treat ments with relatively short intervals is emphasized. The laryngeal mucosa should be as dry as possible before pplying the podofyllinum solution.

All three patients have retained normal configuration of their larynx. The functional result is good with a natural voice. There is no sign of relapse although the last treatment took place several years ago in all cases.

It is not maintained that local application of podofyllinum is a sal tary treatment in all cases of juvenile larynxpapillomas, but it hould be tried as an alternative The ffect of podofyllinum is ttributed to its cytostatic action. The newer cytostatic drugs Proresipar and Proresidor (Sandox) are derived from podofyllinum. There are still no reports on their use i laryngeal papillomas, but it is thought to be worth trying them in the future.

Address. Namdal Sykehus, Namsos.

H Björk Helsinki, Finland.

In 1956 Chr Weber and I reported on 117 cases f laryngeal papilloma treated at th Oto-laryngologic Hospital, University of Helsinki. Observation of the course in the individual cases led to the definite conviction that cure must be related t the absence or development of immunity against the virus infection which is the cause of juvenil laryngeal papillomatosis (and of skin warts). A few years ago, I saw dramatic case illustrating this kind f immunization. The laryngeal papillomas had extended down to th trachea and bronchi. The last incomplet excision was performed as an emergency operation because the patient was at the point of suffocation. This intervention resulted in sudden turn in the course; the papillomas disappeared entirely and the patient has been symptom-free since then.

Podophyllin has been used earlier in papillomas of the larynx. Because of the capricious course of the disease there is good reason t judge critically the effect of different methods of treatment. One thing is certain: irradiation should not be used T my knowledge th only cases reported of malignant degeneration in juvenile papillomas f th larynx had previously received roentgen therapy — Solitary primarily malignant laryngeal papillomas occur in middle-aged and old patients, but these are cases of true neoplasm — disease other than juvenile papillomatosis.

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CURRENT PROBLEMS OF LARYNGEAL CANCER I

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The typical case of laryngeal cancer is male aged 40 or over who has a tendency to prolonged upper respiratory infections, a history of smoking for over 20 years, and bad untreated teeth

The etiology of carcinoma of the larynx has recently been the subject of study in Finland. The material consists of all cases of laryngeal cancer recorded in the period 1959—1963 at the Helsinki University Otolaryngological Hospital and Department of Radiology the Department of Otolaryngology of the University Central Hospital, Turku and the Cancer Register Helsinki. These totalled 191 men and 6 women

For control purposes a big industrial concern kindly gave us access to their employees. The control series thus obtained, consisting of 340 women and 208 men, was selected so as to be as far as possible comparable with the cancer group Table 1 shows the sex distribution in the cancer and the control series.

TABLE 1

CANCER PATIENTS AND CONTROL SUBJECTS CLASSIFIED BY SEX

	Sex distribution	
	Patients %	Control series %
Men	97	38
Women	3	62

The disadvantage caused by the great female preponderance in the control group can be eliminated by using only the men of the control series in the comparison. Another drawback, however is the marked disparity in age and occupational distributions. While the cancer patients consisted mainly of rural population, the control subjects were mainly industrial workers. The difference in age distribution appears in Table 2.

TABLE 2

CANCER PATIENTS AND CONTROL SUBJECTS CLASSIFIED BY AGE

Age years	<30	30—39	40—49	50—59	60—69	70—79	80	?	Total
Male patients		6	39	68	52	18	3	5	191
Controls, men	63	68	53	15	7	1	1	—	208

A detailed questionnaire was completed for both the patients and the controls; special attention was given to factors of possible significance from the point of view of the etiology of carcinoma. The most important observations are reported below

Occupation

The majority or 148, of the cancer patients were manual workers in various occupations Twenty two were non-manual employees, and 21 were executives.

Sex and age

Of the patients, 97% were men, which indicates that males have a definitely greater tendency to cancer of the larynx. The age distribution shows that this is a disease of late middle age and old age

Upper respiratory symptoms

TABLE 3

UPPER RESPIRATORY SYMPTOMS AMONG THE CANCER PATIENTS AND THE CONTROL SUBJECTS

	Patients %	Control series (men) %
Prolonged hoarseness	80	2
Difficulties in swallowing	42	2
Rhinitis	14	9
Cough	39	4

Protracted cough was a symptom in 39% of the male patients and 4 / of the male controls. Hoarseness was complained of by 80% of the patients and by only 2 of the male control subjects. It is difficult to draw a definite line between hoarseness due to a possible laryngitis preceding cancer and hoarseness due to carcinoma itself, but it seems a likely assumption that laryngitis productive of hoarseness had occurred in the cancer patients much more frequently than in the male controls. Smoking, especially cigarrettes, also seems to play a part. Hoarseness of long duration is not only a sign of cancer but also of potential risk of cancer Difficulties in swallowing were experienced by 42% of the cancer patients and by 2% of the male controls. Evidently these difficulties, like the hoarseness, are largely attributable to an already existing tumour in its early stages

Use of voice

On the assumption that overuse of the voice might be a factor in causing laryngeal cancer the patients and the controls were asked about this matter Of the patients, 19% reported overuse of voice at work whereas the corresponding figure for the male control subjects was 14%, which indicates that this factor does not seem to be of essential importance in the production of cancer

Smoking

The incidence of smoking among the cancer patients and the control subjects is presented in Table 4

TABLE 4

CANCER P TIENTS AND CONTROL SUBJECTS CLASSIFIED BY SMOKING

	Patients %	Control series (men) %
Non-smokers	4	35
Smokers or ex-smokers	95	61
\ data	1	4

It shows that the former include a considerably greater number of smokers: indeed their proportion is as high as 95 %.

Age when started smoking

TABLE 5

AGE WHEN STARTED SMOKING AMONG THE CANCER PATIENTS AND CONTROL SUBJECTS

Age, years	Under 10	10—14	15—19	20—24	25—29	Over 30	No dat
Patients	3%	10%	55%	17%	4%	4%	8%
Male controls	2%	19%	49%	18%	7%	3%	2%

Age at the time smoking was started is no distinct differential factor

History of smoking

TABLE 6

CANCER PATIENTS AND CONTROL SUBJECTS CLASSIFIED BY DURATION OF SMOKING

Duration of smoking, years	1—9	10—19	20—29	30—39	40—49	50	No data
Patients	2%	4%	20%	33%	25%	6%	10%
Controls (men)	23%	33%	33%	6%	3%	1%	2%

Because of the fact that the men in the control group were on an average younger the smokers in that group could not possibly have as long a history of smoking as the cancer patients, who were on an average older However the very sharp rise seen in patients who had smoked for 20 years or longer indicates to some extent the part played by a long history of smoking in the development of laryngeal cancer

Amount smoked

TABLE 7

AMOUNT SMOKED BY CANCER PATIENTS AND BY CONTROL SUBJECTS

	Less than 20 cig./day	20 cig. or more/day
Patients	37%	63%
Male controls	49%	51%

A comparison shows that both the number of smokers and the amount smoked was higher in the group of cancer patients. Naturally a long history of smoking adds further to the effect.

Alcohol

Those who reported that they used alcohol accounted for 85 % of the cancer patients and 76% of the controls. Neither these percentages nor the amount of alcohol ingested indicated any distinct difference between the two groups.

Teeth

Of the cancer patients, 11% had good or comparatively good teeth. This figure was correspondingly 72% for the male controls and 70% for the whole control group. The cancer patients included 70% who were edentulous as against 21% for the male control subjects. 46% of the patients and 74% of the controls had brushed their teeth regularly.

It is difficult to demonstrate a causal relationship between a given factor and cancer because there are always a number of additional factors, which cannot all be considered, and these may essentially affect the matter. This study was not designed to prove conclusively that laryngeal cancer is due to smoking. Its purpose is to record the results which are clearly apparent from a study of the etiopathogenesis of the disease concerned. The observations were as follows:

1. There were no particular occupational groups showing a marked tendency to laryngeal cancer.
2. Since 97% of the patients were men, laryngeal cancer shows a definite sex trend.
3. Upper respiratory infections of long duration were clearly more common among the patients than in the control group. Hoarseness was especially frequent in the group of patients, but it seems that cancers already existing were partly responsible for this symptom.
4. There was no correlation between overuse of voice and laryngeal cancer.
5. 95% of the cancer patients, e.g. all six women, were cigarette smokers. There were far more smokers among the patients than in the control group (men).
6. The age at which smoking was started was no differential factor.
7. Of the patients with laryngeal cancer 84% had been smoking for 20 years or longer. The corresponding figure for the control subjects was definitely lower (43%).
8. The amount smoked was slightly greater for the cancer patients than for the control subjects but the difference was not significant.
9. There was no difference between the two groups as regards alcohol ingestion.
10. Compared with the control group the teeth of the cancer patients were definitely in worse condition. There was also a distinct difference in regard to dental care: oral and dental hygiene had been much poorer in the former group.

The fact that the control subjects were younger may play some part in observations 3, 7 and 10.

Conclusions

The typical case of laryngeal cancer is a male aged 40 or over who has a tendency to prolonged upper respiratory infections, a history of smoking for over 20 years, and bad untreated teeth.

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CURRENT PROBLEMS OF LARYNGEAL CANCER II

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The primary radiotherapy of the larynx tumour with or without radical neck dissection is discussed in cases of laryngeal cance with no palpable nodes.

The prognosis of laryngeal cancer depends greatly on whether or not metastatic spread occurs. The presence of distant or cervical metastases increases the gravity of the prognosis considerably Hence it is of great importance, in treating primary cancer of the larynx, to try to prevent as far as possible the occurrence of metastases. In cases in which there are not yet any palpable cervical lymph nodes, the physician in charge must decide whether any prophylactic measures should be adopted with a view to preventing possible late metastases. Active measures that may be considered are operative treatment — so-called systematic or elective »neck dissection» — or prophylactic radiotherapy

In order to determine how much risk there is of metastatic spread by lymph stream to the neck, we studied the rate of metastasis in 114 cases of cancer of the glottis or supraglottis, in which the lymph channels had not been subjected to surgery In these cases the primary laryngeal cancer had been treated by radiation or operation, which latter was followed by roentgen therapy viz. a full tumour dose to the area of the larynx but considerably less to the lymph channels of the neck. Of the cases, 69 were supraglottic cancers and 45 primary cancers of the glottis. In about 25 % of the former and about 5 of the latter there was a recurrence on the affected side in the form of cervical metastasis. On the contralateral side, metastases to the neck occurred in 6* of the patients with cancer of the supraglottis and in 2 of those with cancer of the glottis.

As regards the pathoanatomical type of the tumours, the supraglottic cases included a greater number of less differentiated forms that did the cancers of the glottis. This fact and the better possibilities of spread by lymph stream probably explain the higher incidence of metastases in the group of supraglottic tumours.

Thus it appeared that, in one fourth of the cases involving the supraglottis, the tumour subsequently metastasized via the cervical lymph channels. No preventive surgical measures were adopted in these cases, and it also proved that postoperation radiation had not been effective in preventing metastases. In the cases of cancer of the glottis the rate of metastasis was much lower and metastatic lesions also occurred relatively seldom on the contralateral side.

Starting from the idea that, in cases of laryngeal cancer our aim should be to attain (1) a cure rate as high as possible, and (2) a maximally effective function, it follows that the treatment should be adopted which is generally agreed to yield

he best functional results with the least risk of recurrence. In this respect the arynx and the cervical lymph channels are dissimilar A metastatic lesion in the cervical lymph channels cannot be successfully treated by radiation but must be treated surgically However in the cases of small tumours of the larynx, if favourably situated, good results can be reached by radiotherapy Treatment presupposes that the area involved by cancer can be determined This is possible with relatively great exactitude as far as concerns the larynx itself but not for the lymph channels. Available methods for evaluating whether or not the lymph channels are affected are highly uncertain. The possibilities of appraising the existence and extent of possible distant metastases are even more uncertain

We have at our disposal fairly reliable means of judging the result of radiation of the larynx itself. That is why in the case of delimited laryngeal tumours of stage I and even of stage II we can take the chance and risk of radiotherapy provided we use such a radiation as enables us later to resort to operation should radiotherapy prove insufficient. It is considerably more difficult to evaluate the result of treatment of the lymph channels on the neck. Obviously the method offering greater certainty should be given preference i.e. surgical removal of the tissues probably affected where recurrence may be expected It has appeared that palpation of the neck is no absolutely reliable method of examination. Palpable nodes, if present, can be either metastases or innocent lymphadenitis. A radical neck operation, on the other hand, can reveal carcinomatous nodes not disclosed by palpation. The prognosis as regards cervical metastases must be based on grounds other than palpation. These grounds are: the site, extent, and histological type of the primary tumour

In certain cases it is difficult to decide on the right order of treatment and on the methods to be adopted. These difficulties present themselves in cases without palpable metastases in which the primary laryngeal tumour can probably be effectively treated by radiation but in which the tumour has spread to or has its original site in the supraglottis, so that the likelihood of cervical metastases by lymph stream is increased. It may be asked whether radiotherapy should then precede radical neck operation, or vice versa Or should part of the radiation dose be given and operation be performed after radiation is discontinued?

Both the primary cancer and possible cervical metastases require treatment without delay

A radical neck operation is a measure which is comparatively devoid of danger and causes fairly little disability in most cases. Radiotherapy can be instituted about two weeks after operation. Therefore it seems advisable in these cases to perform first a neck dissection on the affected side, followed by radiation to the laryngeal tumour and later possibly by operation on the lymph channels on the contralateral side. Whether further radiation of the surgically treated side will be needed seems to depend on possible cancer-positive findings in surgical specimens, on the radicalness of the operation, and on other circumstances likely to affect the prognosis.

Anti-cancer chemotherapy may be used while the patient is at hospital for radical neck dissection and awaiting radiation.

Since it has now proved of value to interrupt the radiotherapy and administer it in two parts, it seems possible to administer half of the radiation dose to the laryngeal tumour and utilize the interval for a radical neck dissection on the affected side.

Summonizing we should like to add that we use radiotherapy in early cases of laryngeal carcinoma when the site and limited extent of the tumour render it improbable that metastasis via cervical lymph channels has occurred. Early vocal cord cancer is a case in point. In the case of tumours primarily situated in or later involving the supraglottis or subglottis the possibilities of spread are better because of the greater number of lymph channels; these cases are treated by radical neck dissection on the affected side, regardless of whether there are any palpable lymph nodes or not. The primary tumour in the larynx is trea[illegible] Total extirpation, partial resection or primary radiation may be chose[illegible] upon the site and extent of the tumour The line of treatment is p[illegible] conferences with radiologists from the Department of Radio[illegible] starts for instance with supravolt therapy the result of treatm[illegible] and if the tumour proves resistant to radiation when half the [illegible] administered, operation can still be decided on.

Whatever treatment is chosen it is important to follow the d[illegible] disease so that, if required, the situation can be re-evaluated and the [illegible] policy changed.

TRANSCONIOSCOPY IN CANCER OF THE LARYNX

WITH SPECIAL REFERENCE TO THE DETECTION OF SUBGLOTTIC EXTENSION

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In a material of laryngeal carcinomas from Karolinska Sjukhuset it was found that in cases of glottic carcinoma with subglottic extension th prognosis is very poor both after surgery and irradiation as compared with cases of glottic carcinoma with supraglottic extension. It is obvious that this poor prognosis is due t diagnostic difficulties, the subglottic extension is difficult to establish by direct laryngoscopy and tomography until it is rather advanced.

A new method, transconioscopy for adequate inspection of the subglottic space is described. Comparative evalu tion of this method on 60 cases of laryngeal carcinoma indicated that the presence of subglotti tumour-extension would have been overlooked in about 50% of the cases if only direct laryngoscopy and tomography had been used.

The prognosis for glottic carcinoma with subglottic extension has been considered to be especially poor (Oeser et al. 1951 Stützer 1957) In a material of laryngeal carcinomas treated at Karolinska Sjukhuset it was found that this poor prognosis is only apparent, and is due to diagnostic difficulties

The subglottic part of the tumour cannot be seen by direct laryngoscopy of the larynx or visualized by tomography until it is quite advanced.

The material comprised all 178 cases of laryngeal carcinoma treated at Karolinska Sjukhuset between 1940 and 1960 that were classified on the basis of direct laryngoscopy and tomography as involving the vocal cords and supraglottic and/or subglottic parts of the larynx.

The treatment consisted in irradiation or laryngectomy with or without neck dissection As a rule the source of irradiation was teleradium and the theoretical tumour dose was 5500—7000 r

The results of the treatment are presented as the 5-year cure rate after the primary treatment and are based on the number of determinant cases that is to say the total number of cases minus the intercurrent deaths.

As Table 1 shows, the results for the subglottic extension and the combined sub- and supraglottic groups were practically the same, and considerably poorer than for the supraglottic group Since the distribution between irradiated and

TABLE 1

RESULTS O THE T[illegible]T

Location	Five-year cure rat	
	%	No.
Supraglottic extension	69	55/80
Subglottic	36	10/28
Supra- and subglottic extension	39	16/41

laryngectomized patients and the frequency of low-grade carcinoma were the same in the subglottic and combined sub- and supraglottic groups it would seem logical to conclude that the poor results were due to the presence of subglottic extension. In the subsequent analysis of the results they were therefore considered as a single group, referred to as subglottic extension

Irradiated cases

TABLE 2

FIVE YEAR CURE RATE AFTER IRRADIATION

	Supraglottic ext.		Subglottic ext.	
	No.	%	N	%
Cord mobility normal	12/17	63	2/8	13
impaired or lost	13/26		1/16	

There was a marked difference in prognosis between the sub- and supraglottic groups of the irradiated cases (Table 2) This difference might conceivably be due to differences between the two groups as regards degree of differentiation, tendency to deep infiltration or size of the tumour However as the ratio of high-grade to low-grade carcinoma is the same for both location groups the difference cannot be due to a difference in the degree of differentiation.

Nor would the explanation seem to lie with the depth of infiltration, for there was a large difference in the results for the two location groups for both superficial carcinomas with normal cord mobility and for deeply infiltration tumours with impaired mobility (Table 2) Infiltration of the cartilage in the subglottic space is not necessarily accompanied by a reduction in cord mobility but deep infiltration into the subglottic space by a tumour growing superficially on the cord must be quite uncommon.

We are thus left with the third explanation, namely tumour size. It is, in fact, highly probable that the difference in the results is due to the tumour being smaller in the supraglottic than the subglottic group for supraglottic, but not subglottic infiltration can be diagnosed at an early stage by direct laryngoscopy The cranial part of the subglottic space is hidden from inspection by the vocal cords and any tumour here will avoid detection until it is large enough to be visualized by radiography It may therefore be inferred that the supraglottic group will contain cases of limited extension that are not included in the subglottic group: early subglottic extension will have been overlooked and the case classed as one of pure vocal-cord tumour

Evidence that this is the real explanation is found in the fact that after irradiation of tumours recorded as being located in the vocal cords there were 41 recurrences, more than one third of which had a subglottic location. In these cases a subglottic extension had probably been overlooked from the outset.

Laryngectomized cases

That the diagnosis of subglottic extension has been inadequate is brought out even more strikingly by the analysis of the laryngectomized cases.

TABLE 3

FIVE YEAR CURE RATE AFTER LARYNGECTOMY

	Supraglottic ext.		Subglottic ext	
	%	No.	%	No
Laryngectomy	73	24/33	50	21/42
Laryngectomy + neck dissection		4/4		2/3

In the laryngectomized cases too there was a large difference in the results for the two location groups.

TABLE 4

RECURRENCE AFTER LARYNGECTOMY

	Supraglottic ext.		Subglottic ext.	
	%	No.	%	No.
Local recurrence	9	3/33	12	5/42
Secondary lymph-node metastases	18	6/33	40	17/42

It is evident from Table 4 that the poor results in the subglottic extension group were due to the high frequency of secondary lymph-node metastases. This is remarkable in view of the fact that in the large series published by Mc Gavran et al. (1961) and Pietrantoni et al (1962) the frequency of lymph-node metastases was always higher for supra-than subglottic carcinoma. In these investigations, however the extension of the tumour was determined histologically after laryngectomy whereas in the present series it was determined on the basis of the clinical findings prior to operation. The high frequency of lymph-node metastases in this series is thus presumably ascribable to diagnosis of the subglottic part of the tumour at a late and advanced stage.

Transconioscopy

From this material it thus seems that direct laryngoscopy and tomography are *inadequate for detecting subglottic extension, and that methods permitting of* direct inspection of the subglottic space should be used One such method is the insertion of an angle telescope into the larynx by direct laryngoscopy (Gustelson et al. 1952, Dietzel, 1954) but this has certain disadvantages, however

The presence of a tumour in the supraglottic region or on the vocal cords can make it difficult if not impossible to place the telescope in the subglottic space (Müller 1954) In the subglottic space the telescope is located extremely close to the mucosa, the field vision is therefore limited and it is difficult for the observer to get a perception of the whole of the subglottic extension of the tumour (Günnel et al., 1964)

To avoid these disadvantages a method which has been designated transconioscopy has been devised at Karolinska Sjukhuset (Mårtensson et al., 1961) The procedure is as follows After local anaesthesia the cricothyroid membrane is

punctured by means of a trocar with an outer casing The diameter of the instrument is 4 mm Through the casing an angle telescope is inserted into the subglottic space

Inspection can then be made of the subglottic space except for the point of puncture and parts of the supraglottic structures. The field of vision of the under surface of the cords is about 10 times as great as that for a telescope inserted through a laryngoscope, and the examination can be carried out even in cases of extensive supraglottic tumours (Mårtensson, 1967)

Clinical evaluation of transconioscopy

Transconioscopy has been used in about 160 cases over a period of about two and a half years. There have been no serious complications; minor haemorrhage into the trachea has been fairly common but it has not interfered with the inspection and has never been severe enough to produce haemoptysis. Circumscribed subcutaneous emphysema has sometimes occurred at the point of pucture. The examination has been tolerated by the patient without complaint.

60 cases of carcinoma of the larynx have been investigated. They were all examined by direct laryngoscopy and almost invariably also by tomography The latter examination was performed before the endoscopy in order to avoid any misleading radiologic appearances due to swelling caused by the endoscopy

The extension of the tumour is presented in Table 5

TABLE 5

Extension	No.	Treatment	
		Surgery	Irradiation
Glottic	23	8	15
+ subglottic	18	10	8
Supraglottic + glottic + subglottic	6	5	1
+ glottic	9	5	4
Supraglottic	6	0	6

The findings recorded for direct laryngoscopi and tomography in glottic tumours and glottic tumours with subglottic extension are summarized in Table 6

TABLE 6

	Direct laryngoscopy	Tomography	Both methods
Subglottic extension wrongly suspected	0/23	1/19	1/23
Subglottic extension overlooked	13/16	/14	7/16

In all 23 cases of glottic tumour it could be seen by direct laryngoscopy that the tumour was growing on the upper surface of the cord to the edge of the cord. Any extension to the under surface of the cord could be inspected only by transconioscopy In the one case in which tomography disclosed a subglottic swelling, transconioscopy showed that it was not due to tumour infiltration.

In only 3 of the 16 cases of glottic tumour with subglottic extension could the subglottic part be inspected by direct laryngoscopy· in these the subglottic tumour was either exophytic or it extended down to the level of the cricoid cartilage. In the other 13 cases only the part of the tumour on the vocal cord could be seen by direct laryngoscopy In 7 of the 14 cases in which tomography was performed no subglottic abnormality was detected The subglottic part of the tumour had been overlooked by both methods in 7 cases. In all the patients the whole subglottic part of the tumour could be inspected by transconioscopy

The direct laryngoscopic and tomographic findings for tumours involving supraglottic parts of the larynx are summarized in Table 7

TABLE 7

	Direct laryngoscopy	Tomography	Both methods
Subglottic extension overlooked	5/6	3/6	3/6
Vocal cord affection	5/15	2/15	2/15
Subglottic extension wrongly suspected	—	3/15	3/15
Vocal cord affection wrongly suspected	—	2/6	2/6

A supraglottic location was established for 21 tumours, and in 6 of these there was a subglottic extension. In only one case this part of the tumour could be inspected by direct laryngoscopy In 3 tomography did not disclose any subglottic abnormality and in these 3 the subglottic part of the tumour was overlooked with both methods. In all 6 cases the subglottic part of the tumour could be inspected by transconioscopy

In 15 cases the supraglottic tumour involved the vocal cords. In 5 of them inspection of the cords by direct laryngoscopy was prevented by the supraglottic part of the tumour In 2 of these tomography revealed no signs of vocal cord affection and with both methods they would have been classed as pure supraglottic carcinoma. In all 15 cases the involvment of the cords was demonstrated by transconioscopy In 3 other cases a subglottic swelling visualized by tomograph was proved by transconioscopy not to be due to tumour infiltration.

In 6 cases the tumour was purely supraglottic. In 3 of them inspection of the vocal cords was impossible and in 2 of these evidence of cord invasion was provided by tomographs. In all 6 cases the caudal border of the tumour was found by transconioscopy to be situated above the level of the cords.

Thus, in 18 out of 60 cases the transconioscopic findings modified the previous view of the extent of the tumour based on direct laryngoscopy and tomography

Subglottic extension was established by transconioscopy in 22 cases. By direct laryngoscopy + tomography it was overlooked 10 times. At operation performed on 15 of these patients the preoperative assessment of the subglottic extension was confirmed in all respects. In no patient undergoing operation was it found that subglottic extension had been overlooked with transconioscopy In several cases subglottic extension suspected on the bases of tomograms was excluded by transconioscopy The method is thus a most reliable one for the diagnosis of subglottic

TABLE 8

	Tumour extension according t	
	Tomography + Laryngoscopy	Tomography + Laryngoscopy + Transconioscopy
Glottic	29	22
		1
		7
Glottic + Subglottic	10	9
Supraglottic + Glottic + Subglottic	6	3
		3
		3
Supraglottic + Glottic	9	4
		2
		2
Supraglottic	6	4

extension of tumours. It also provides a means of inspecting the caudal part of a supraglottic tumour that is often hidden from view by direct laryngoscopy

Transconioscopy is evidently a most valuable supplement to other methods of endolaryngeal diagnosis, and is indicated when a tumour involves, or is suspected of involving, the vocal cords. If such involvement is established by direct laryngoscopy subglottic extension can be detected by transconioscopy with this method, moreover it is possible to inspect cords hidden by a supraglottic tumour

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5 YEARS SYMPTOM-FREE SURVIVAL RATE OF 414 CONSECUTIVE CASES OF LARYNGEAL CANCER REFERRED TO THE RADIUM CENTRE COPENHAGEN

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The results of treatment of 414 patients suffering from laryngeal cancer referred to the Radium Centre of Copenhagen have been recorded according to anatomical localization and stage of the disease

The choice of treatment has in most cases been made after joint consultation between the laryngeal surgeons and the radiotherapist in charge

Apart from patients with complete fixation of the chords, or subglottic localization of the disease, the primary treatment has usually been roentgen irradiation.

During the 12 years period 1948—1959 438 patients suffering from laryngea cancer were referred to the Radium Centre in Copenhagen. This report concern the treatment results of the 414 patients who were referred without having bee given any previous treatment.

The treatment policy has been that formulated by the late professor Jen Nielsen in 1912, in cooperation with the laryngeal surgeon, Dr Falbe-Hansen (Jens Nielsen, 1951) In accordance with this policy most of the patients have bee given radiation (180—250 kV) as a primary treatment with the object of obtainin optimum results, i.e., the highest number of cures, with a maximum of preservatio of normal voice The majority of the patients have been seen at the Radiun Centre at joint conferences by prof Jens Nielsen and Dr Falbe-Hansen, the EN clinic, Kommunehospitalet, Copenhagen, and prof H K Kristensen, the EN clinic Rigshospitalet. The choice between surgical and radiological treatment ha been made at these conferences, and primary operation has been adviced to al biologically operable patients with subglottic cancer or fixed chords.

Table 1 gives an account of the results obtained in all 414 patients treated including the palliative ones. The clinical material is grouped according to th site of the tumour and comprises 131 supraglottic (31%) 260 glottic (63%) an 23 subglottic cancers (6 %).

39 patients were women 14 supraglottic, 21 glottic and 3 subglottic.

In some cases it was difficult to determine the primary localization of the lesio at the first examination Most of the patients were irradiated and in these case the regular observation of the regression of the tumour towards its point of origi made possible an accurate anatomical classification

By this conservative treatment policy 51 of all patients treated have survive symptom free for 5 years or more

If one includes only «determinant» cases, by excluding those patients survivin symptom-free less than 5 years, the cure rate increases, especially for the glotti cancer cases Of these 81 of the «determinant» cases survived symptom-free compared with 68 of the total number

TABLE 1

RESULTS OF TREATMENT IN 414 CASES OF LARYNGEAL CARCINOMA
Radium Centre Copenhagen 1948—1959

Site	Total no of cases	All symptom-free over 5 years				Dead		Determinant
		X-ray alone	Primary surgery	Surgery for rec. or persist.	Total X-rays + surgery	S-free less than 5 years	With cancer	S-free over 5 years of patients examined → 5 years
Supra-glottic	131	22/79	2/13	17/39	41/131 (31%)	11	79	41/120 (31%)
Glottic	260	126/172	16/37	35/51	177/260 (68%)	48	33	177/212 (84%)
Sub-glottic	23	1/4	4/16	1/3	6/23 (26%)	4	13	6/19 (31%)
					224/414 (54%)			224/351 (64%)

In accordance with the treatment policy already described only 66 patients were primarily operated, and of these about 2/3 had postoperative irradiation. In addition, 93 patients were operated on after primary irradiation, either for persistent or recurrent tumour Thus operation made a contribution to the result in 46 of the 41 supraglottic cancer cases surviving symptom-free for 5 years or more, (12 total laryngectomies). Of the 177 glottic cancer cases, surviving symptom-free 5 years or more, 51 cases or 28% were operated on (28 total laryngectomies). When the 3 groups of survivors are considered however the highest percentage of surgical operations was performed on those with subglottic cancer i.e. in 6 survivors 3 had total laryngectomy and 2 had partial (anterior) laryngectomy

The main question to be answered concerning the policy chosen, must be: has the chance of 5 years survival in operable cases been jeopardised by the use of radiation as the primary treatment with the object of preserving a normal voice?

In Table 2 is shown the total number of glottic and supraglottic cancer cases operated after primary radiation according to the extent of the disease beyond the point of origin (U.I.C.C. 1958)

Of the 223 glottic cancer cases, T 1 T 4 primarily irradiated, 51 had to be operated. Of the 11 glottic cancer cases, that were operated on for persistent tumour 7 or 64% lived symptom-free for more than 5 years. Of the 40 glottic cancer cases, that were operated on because of recurrence, 31 or 77% survived symptom-free for 5 years or more These cure rates may seem low in comparison with the cure rate of 68% for the total group (Table 1) since this includes some palliative treatments, but the number of patients operated on after primary irradiation is really too small to allow comparison with the total group If one considers only the 23 glottic cancer cases in stages T 1 + T 2, that had to be operated after primary irradiation, 22 or 78% lived symptom-free for more than

TABLE 2

OPERATIVE RESULTS IN LARYNGEAL CANCER PRIMARILY IRRADIATED (X RAY)

Extent	Glottic				Supraglottic			
	Survival symptom-free over 5 years				Survival symptom-free over 5 years			
	Total opr of total lrr	Opr for persistant tumour	Opr for recurrent tumour	T tal	T tal opr f total lrr	Opr for persistant tumour	Opr for recurrent tumous	Total
T + T T T_4	28/153 22/65 1/3	3/4 4/6 0/1	19/21 12/16 0/0	22/23 16/22 0/1	6/13 5/10 14/46	1/3 1/2 7/13	3/3 1/3 1/1	4/6 2/5 8/11
	51/223	7/11 (61 %)	31/10 (7 %)		25/60	9/18 (50 %)	5/7 (71 %)	
T +,N + + T N_1+ + T_4 N +,+	0/1				4/8 2/5 8/30	0/2 0/1 1/4	1/2 0/1 1/1	
	0/1 51/221				14/49 39/118	1/7	2/7	

5 years. However 4 of the 28 patients died symptom-free before 5 years had elapsed. Two died symptom-free 1¼ and 3¼ years after partial laryngectomy for persistent tumour and 2 died symptom-free after operation for recurrent tumour one 2 years after total laryngectomy and the other 3 years after partial laryngectomy Thus 22 or 92 / of the 24 determinant cases of glottic cancer who were operated after primary irradiation, lived symptom free for more than 5 years, and this seems comparable to the 95 / survival of the determinant cases for the whole group (Table 3)

From Table 1 it is established that the 5 year survival of cases of supraglottic and especially subglottic cancers is poorer than that of glottic cancer cases. Table 3 shows the effect on the prognosis when there is extension of the cancer from the glottic site either into the supraglottic or the subglottic region. It is seen

TABLF 3

SI IFICANCE EITHER INFRA SUPRAGLOTTIC EXTENSION OF GLOTTIC CANCER

Extent	No. of cases	Alive symptom free ver 5 years				Determinant
		X-rays alone	Primary surgery	Surgery for rec. or persist.	Total x-rays + surgery	S-free over 5 years examined→5 years
Glottic T + T	151	96/125	0/1	22/28	118/154 (77 %)	95 %
Glottic T inv subglot	41	16/23	4/11	5/7	25/11 (61 %)	69 %
Glottic T inv supra glottic.	28	9/15	2/1	7/9	18/28 (61 %)	90 %
Subglottic T + T + T_4	23	1 1	1/16	1/3	6/23 (26 %)	31 %

that extension of the disease beyond the true vocal chord diminishes the survival rate. In stages T 1+T 2 when the disease is confined to the glottis, the symptom-free survival rate is 77%. When extension occurs above or below the survival rate is diminished to about the same extent namely 61% in stage T 3 (subglottic) and 64% in stage T 3 (supraglottic) When »determinants cases are considered these percentages become 69% and 90%, the prognosis appears to be worse in subglottic extension, but the prognosis in supraglottic extension seems to be similar to the prognosis when the tumour is confined to the glottis (T 1+T 2) 95% and is quite different to that applying to cancers arising in the supraglottic region (all stages: 58%)

Dr B Mårtensson reports a more pronounced effect on the prognosis of subglottic extension, but the reason why this effect is not seen so obviously in this series may be the fact that 8 of the 41 cases involved, were females. 7 of these 8 females survived symptom-free for more than 5 years. In 1961 Lederman pointed out that the prognosis for laryngeal cancer is better in female patients. This seems to hold true in this series.

The prognostic significance of decreased mobility has been estimated in Table 4 Since most glottic cancers with fixation of one or both vocal chords were T 3, a comparison has been made of the outcome of treatment in all T 3 glottic cancer cases grouped according to mobility 1) free mobility including those cases, where the tumour mechanically prevents complete adduction, 2) decreased mobility where abduction is distinctly reduced, 3) complete fixation of one or both vocal chords. The numbers are small, but it seems that truly decreased mobility should be taken as a bad prognostic sign. Such cases should therefore be regularly observed more frequently than the routine which is usually every 2 months.

At the Radium Centre patients are followed up at regular intervals as long as they live. It appears that in the period concerned in this report, some 11 patients developed recurrence later than 5 years after the original treatment, 8 in the glottic group 1 in the subglottic group and 2 in the supraglottic group Of these 11 patients Dr Falbe Hansen in another paper will report in detail on 8. Here it

TABLE 4

SIGNIFICANCE OF DECREASED MOBILITY FOR RESULTS OF [illegible]LOTTI CARCINOMA

Mobility	Alive symptom-free over 5 years				Total X-rays + surgery	Determinant
	No. of cases	X-ray alone	Primary surgery	Surgery for rec. or persist.		S-free over 5 years of patients examined→5 years
free	63	27/36	6/12	11/15	44/63 (70%)	44/54 (81%)
decreased	11	1/5	0/3	1/3	2/11 (18%)	2/7 (28%)
fixed	25	1/5	7/15	4/5	12/25 (48%)	12/19 (63%)
					14/36 (38%)	14/26 (54%)

will only be pointed out that the recurrences developed 5—13 years after the primary treatment, and that in all but one the mode of treatment was irradiation. Of the 11 recurrences 9 were operated on and 2 were irradiated One died with recurrent cancer 3 years later and the other is still alive symptom-free 1 year after cobolt irradiation.

This report is only concerned with results obtained by the conservative treat ment policy outlined and using Roentgen radiation at 180—250 Kv Larger groups of patients suffering from laryngeal cancer have been treated according to the same principles in Therapy Centers, where radiation at higher energies is available. Because of the skin and cartilage sparing effect of this type of irradiation higher doses of irradiation have been applied, and the treatment results in the more advanced cases of laryngeal cancer have thereby been improved (Lederman 1961 Wang et al. 1963)

Since 1959 Cobalt units have been in use at the Radium Centre of Copenhagen, and an increasing number of laryngeal cancers have during this time been treated by high voltage irradiation. This report on patients treated in the period from 1948 to 1959 is thus mainly of historical interest. In spite of this fact I hope that the results obtained have justified our treatment of laryngeal cancer according to the principles first laid down by Coutard

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END RESULTS OF RADIATION THERAPY OF LARYNGEAL CANCER

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A total of 1284 new patients with laryngeal cancer were registered at the Radiotherapy Clinic in 1936—1959. 949 patients have been followed up for at least 10 years. 869 of them were treated, 653 with X-rays and 216 with surgery and postoperative X-ray therapy. The material was analysed according to the usual clinical staging, the TNM system and the topographical localisation of the tumour. The 5-year result was 38.5 per cent for the total material, the 10-year result was 23 per cent. In early cases, radiotherapy gave equally good results as combined surgical-radiologic treatment. Radiation therapy in addition, preserves the patient's voice. Combined therapy gave a more reliable result in more advanced cases. The material shows clearly that the results of radiotherapy have improved in the course of 20 years. The proportion of earlier stages has grown year by year and patients now seek therapy in an earlier stage than they did in the 1930s and 1940s.

An important advantage of radiation therapy over surgery in the treatment of laryngeal cancer is preservation of the voice. It has therefore been recommended that all early and moderately advanced cases of laryngeal cancer be treated by radiotherapy (Lederman 1961, Taskinen & Holsti 1966). A preliminary course of radiotherapy may be of value also in advanced cases for which surgery is the principal treatment (Lederman 1961, Taskinen & Holsti 1966). Indeed, the main function of radiotherapy in the management of carcinoma of the larynx is to reduce the number of laryngectomies as much as possible, as Cantril (1960) pointed out. A 5-year survival rate was achieved in 50 per cent of a material treated by radiation therapy alone in 1955—1959 (Taskinen & Holsti 1966). The purpose of the present paper was to report the preliminary long-term results of X-ray treatment of laryngeal cancer.

Clinical material and treatment methods

A total of 949 new patients with laryngeal cancer were registered at the Radiotherapy Clinic in 1936—1955. 653 of them were treated primarily with X-rays and 216 were given post-operative roentgen therapy. 80 were not treated at all at our clinic (Table 1). Five patients were lost to follow-up.

Table 2 shows the topographic distribution of 861 treated cases followed up for 10 years. The majority of the patients had supraglottic cancer. »Unknown» refers to cases on whom total laryngectomy had been performed prior to their arrival for radiation therapy but whose primary status had not been stated accurately.

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TABLE 1

CANCER OF THE LARYNX TREATED IN 1936—1955

X-ray therapy	653
Combined surgery and X-ray therapy	216
Not treated	34
Consultation. Send to other hospitals for treatment	40
Other tumours than carcinoma	6
Total	949

TABLE 2

TOPOGRAPHIC DISTRIBUTION OF THE TREATED CASES

Supraglottic	532	62.0 %
Glottic	29	31.0 %
Subglottic	6	0.7 %
Unknown	29	3.3 %

Patients with vocal cord cancer generally sought treatment in a more favourable phase than the supraglottic cases. Twenty nine per cent of the glottic cancers were of grade I 29 per cent grade II 37 per cent grade III and 5 per cent grade IV the corresponding percentages for supraglottic cancer were 5 23 47 and 25 The incidence of metastases in glottic tumours was 15 in supraglottic 30 per cent

For comparison of different therapeutic methods and results achieved at different clinics it is important that the cases are classified not only topographically but also clinically according to an internationally accepted method of classification. The TNM classification gives the best basis for analysis of both the effects of the spread of the cancer and the influence of regional lymph node metastases and distant metastases on the results (Caulk 1966 Taskinen & Holsti 1966). Clinical distribution into 4 grades is often sufficient for practical purposes but even then it is necessary to follow generally accepted criteria

All the patients treated with radiation received roentgen therapy The technique has been described in detail elsewhere (Taskinen & Holsti 1966) The total tumour dose was 5000– 5500 R in 25—35 days. The patients generally developed mild epithelitis which was followed at the weekly mirror examinations. More severe radiation reactions were rare

RESULTS

The 5-year result for the treated patients in the total series was 38.5 per cent and the 10-year result 23 per cent (Table 3) The absolute 5-year cure rate for all the 949 patients registered at the clinic was 35 per cent and the 10-year cure rate was 21 per cent It can be seen from the table that the results were definitely better in glottic than in supraglottic tumours. An important reason for this is that glottic tumours give earlier symptoms and thus these patients come for treatment in a more favourable phase. The results at our clinic have improved in

TABLE 3

LONG TERM RESULTS IN THE WHOLE SERIES

	All cases	Supraglottic	Glottic
5 years	38.5 %	33 %	47 %
10 years	23 "	19 "	31 %

TABLE 4

THE IMPROVEMENT OF 5-YEAR RESULTS OF X-RAY THERAPY IN THE COURSE OF YEARS

1936—1942 (Mustakallio)	25 %
1950—1951 (Voutilainen & Tuovinen)	34 "
1955—1959 (Taskinen & Holsti)	50 "

the course of the years (Table 4). The decisive contributory factor has been the improvement of early diagnosis. Cases of grades I—II totalled only 8 per cent in 1936—1942 but 55 per cent in 1955—1959

The treatment methods and the 5- and 10-year survival rates according to them can be seen in table 5 A more detailed analysis is given in table 6 which shows the results achieved by combined surgery and post-operative roentgen therapy and by roentgen therapy alone in the different grades of spread and topographic groups. In group T_1N the results of the two methods were roughly similar for

TABLE 5

RESULTS ACCORDING TO TREATMENT METHOD

Treatment	Patients	5-year survival	10-year survival
Partial resection + X-ray	109	6[illegible] (62 %)	42 (39 %)
Total laryngectomy + X-ray	107	51 (48 %)	35 (33 %)
X-ray therapy alone	653	214 (33 %)	122 (19 %)
Total treated	869	332 (38.5 %)	199 (23 %)
registered	949	332 (35 %)	199 (21 %)

TABLE 6

LONG TERM SURVIVAL IN DIFFERENT STAGES ACCORDING TO TOPOGRAPHY AND TREATMENT METHOD

	Supraglottic		Glottic	
	Combined	X-ray	Combined	X-ray
T N				
5 years	5[illegible] "	62 "	71 %	68 %
10 years	33 "	33 %	55 "	61 %
T_2N_0				
5 years	58 %	50 %	[illegible]8 %	38 %
10 years	53 %	37 %	63 %	39 %
T_3N_0				
5 years	60 %	31 %	33 %	33 "
10 years	44 %	18 "	25	8 %
T N				
5 years	38 "	31 %	33 "	[illegible] %
10 years	31 %	21 %	0 %	

both glottic and supraglottic cancers. In cases T_3N_0 the results of combined therapy were slightly better especially for glottic tumours The results of combined therapy were definitely superior to those of roentgen therapy alone in cases T_3N_0. In group T_4N_0 the results were extremely poor for glottic tumours, but the prognosis was still fair for supraglottic tumours with both combined therapy and roentgen therapy alone; 38 and 34 per cent, respectively of the patients with tumours that had infiltrated the base of the tongue and the piriform fossa survived 5 years.

The effect of regional lymph node metastases on the deterioration of prognosis is distinct. In the N group the results of combined therapy and roentgen therapy alone were 59 per cent contra 42 per cent, and in glottic tumours 63 contra 50 per cent. The results were considerably poorer in the N_1 group already to say nothing of groups N_2 and N_3.

None of the cases with distant metastases survived 5 years. Therapy was purely palliative in these cases.

DISCUSSION

Except for the early stages, the results obtained in the present material by combined surgery and post-operative roentgen therapy were better than those achieved by roentgen therapy alone. This finding confirms earlier experience at our clinic (Voutilainen & Tuovinen 1962) Radiotherapy was generally administered 1—2 months after the operation. We have no experience yet of pre-operative radiation therapy which has gained increasing support in the last few years and is also more sensible radiobiologically than post-operative radiotherapy (Bloedorn 1962). Radiation therapy as the first method of management offers many advantages. Firstly it gives good results in the early stages of the disease (Lederman 1961 Lauerma & Siirala 1962, Jolles 1966, Taskinen & Holsti 1966) Secondly it is still easy to operate for post radiotherapy recurrence, whereas radiation therapy is rarely of curative value in a post-operative recurrence. Especially for the preservation of function, radiation therapy should be administered first in early and moderately advanced cases, leaving surgery to be used for possible recurrences (Lederman 1961 Bohndorf & Dickhaeuser 1966). It has been noted that 75 per cent of the patients with laryngeal cancer who had survived 5 years and been treated primarily with roentgen had a good or fairly good voice (Taskinen & Holsti 1966).

The conclusions to be drawn from the present preliminary study on long-term results are that.

1 Early diagnosis is the most important factor for the improvement of results;
2. Radiation therapy gives equally good results as combined surgical-radiologic treatment in incipient cases. Radiation therapy also preserves the patient's voice·
3 Combined therapy gives a more reliable result in more advanced cases;
4 Mobile cervical gland metastases should be operated on and neck dissection should be performed in these cases.

5. The therapeutic results in laryngeal cancer are not yet optimal. Better results can be anticipated with the development of radiologic-surgical combination therapy — megavoltage therapy in fact offers a good chance of surgical management even after radiotherapy — or radiotherapeutic fractionation methods which are better from the tumour biologic and radiobiologic standpoint.

The present authors are currently studying both these aspects. It is in the patient's interest that surgery and radiotherapy do not compete. The laryngologist and radiotherapist should co-operate and decide on the therapeutic principles together. The good collaboration between the ENT clinic and the Radiotherapy clinic in Helsinki has been extremely valuable.

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LATE RECURRENCES OF LARYNGEAL CANCER WHICH HAD BEEN TREATED EXCLUSIVELY BY COUTARD IRRADIATION OR BY OPERATION PLUS IRRADIATION

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Eleven cases of late recurrences (i.e. recurrences appearing more than 5 years after apparent cure) of laryngeal cancer following X-ray irradiation, or operation plus X-ray irradiation, were analysed with a view to the site, extent, and microscopical appearance, etc. of the cancer. No correlation was found between the development of the recurrence on the one hand and the patients' ages, the dose of X-rays, or the site and stage of the primary cancer on the other.

More than 30 years have passed since fractional X-ray irradiation by the method of Coutard was introduced as the standard treatment of laryngeal cancer in the Radium Centre, Copenhagen.

This treatment was used (in some cases combined with surgery) until 1950 when a high-voltage unit was purchased.

Since that time high voltage irradiation has been employed in treating cancer of the larynx in the predominant number of cases, especially the more extensive ones.

All patients who have been treated for cancer in the Radium Centre are followed for the rest of their lives, also after they have been free of recurrence for 5 years after the completion of treatment. We, therefore, know how these patients fare — also at long sight.

In some cases we have diagnosed recurrences in patients who have been symptomless for many years and apparently cured of their cancer. These cases are of interest for practical as well as theoretic reasons. Since the literature seems to be fairly silent on this point, we analysed a 16 year material with a view to late recurrences, i.e. recurrences appearing more than 5 years after apparent cure.

This material is derived from the years 1935—1950. During this period a total of 140 patients, 10 females and 130 males, with cancer of the larynx were treated.

In analysing the material we found that 11 patients developed recurrences more than 5 years after the completion of treatment. These recurrences became manifest from 6 to 18 years, on an average 11 years, after the primary treatment.

All the patients were males who had been from 40 to 71, average 55 years of age, at the completion of primary treatment.

The primary treatment had consisted in 9 cases in fractional X ray irradiation by the Coutard method, in one case in hemilaryngectomy combined with postoperative irradiation, and in one case in total laryngectomy with pre- and postoperative irradiation.

The dose of X-rays ranged from 3 070 r to 10 100 r average 6 460 r

The site of the cancer was in 6 cases the true vocal cord, in 4 cases the vestibule of the larynx, and in one case the subglottis.

In respect to staging, we used that introduced by Jens Nielsen in 1941 According to this classification, 6 cases had been in Stages I—II and 5 in Stages III—IV

Histologic examination of the primary tumours had in all 11 cases shown solid parakeratotic carcinoma.

Three patients had two recurrences, at 12, 4 and less than one year s interval.

In the following analysis, however regard is paid only to the former of the late recurrences.

In the 9 patients who had primarily been treated with X-rays only all the recurrences appeared in loco In the patient who had had primary hemilaryngectomy it also occurred in loco while in the patient who had primarily undergone total laryngetomy the recurrence appeared in the hypopharynx on a level with the site of the larynx and in the soft tissues of the neck. *In addition to the local* recurrence one patient also had pulmonary metastases.

The treatment of the recurrence was in 6 cases total laryngetomy in one case hemilaryngectomy in two cases laryngofissure with chordectomy and in one hypopharyngectomy and in one case repeated irradiation.

The patients ages after treatment of the recurrence were at follow-up in the spring of 1966 (or at death) 57 to 96 years, average 70 years. In other words, the average age was 15 years older than at the time of primary treatment.

The results of treating the recurrences were as follows. Six patients were alive without recurrence more than 5 years after the treatment one was alive free of recurrence at 3 years, one was alive with a recurrence at 2 years, two had died of recurrence before the expiration of the 5-year period, and one had died of coronary thrombosis a few months after the treatment (laryngectomy)

Discussion

As our series comprises only patients whose disease had been treated with X-rays (alone or combined with surgery), we have no experience in respect to the recurrence rate in patients whose primary and only treatment has been surgical.

True late recurrences following radiotherapy are rare, but nevertheless more common than we had assumed. It is a particular cause for wonder that recurrences may arise as late as 18 years after apparent cure.

We tried to relate the development of the recurrences to the patients ages, to the primary site of the cancer and its stage and to the dose of X-rays, but without finding any correlation.

It is particularly worthy of note that small cancers on the true vocal cords, treated with relatively low doses of X-rays (3 000 r — 4 500 r) may recur — even up to 14 years after apparent cure.

Owing to the small numbers involved, we did not investigate the recurrence rate within stages I—II and stages III—IV of the original series of 146 patients.

The treatment of late recurrences should presumably be surgical whenever possible In our series 9 of the recurrences could be treated by a radical operation. In the tenth operated patient there was a recurrence in the hypopharynx, arising 18 years after total laryngectomy plus pre- and postoperative irradiation In this case it proved impossible to perform radical surgery as there was diffuse infiltration by the tumour in the soft tissues of the neck.

The prognosis of late local recurrences has proved has proved to be quite good in cases which have lent themselves to radical surgery

As regards the genesis of the late recurrences, there are theoretically several possibilities.

The idea which first suggests itself is that the X-rays which had been administered in all the cases, are responsible. That X ray irradiation may have a tardive carcinogenic effect has been claimed by several workers, i.a. Baclesse (1949) *Dancot et al. (1965) and Holinger and Rabbet (1953) Since our series includes* only recurrences of the same histologic architecture as the primary tumours, and since practically all the recurrences appeared in loco it might also be imagined that the recurrences had arisen from epithelial tissue which had been left behind but which possessed potential carcinomatous properties which have not manifested themselves until this late juncture. Late recurrences of laryngeal cancer treated by operation only (Svane-Knudsen, 1960) are most naturally explained by the assumption of such potentially carcinomatous cells which have been left behind

The fact that in some cases recurrences may develop so late goes to show the necessity of a close follow-up on the patients as long as they live. Such follow up is practicable in a small country like Denmark, but it is difficult, if not impossible in the large populations. The importance of regular follow-up is emphasized by the favourable prognosis of the recurrences, if they are within reach of radical surgery at the time when they are diagnosed.

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VOICE AERODYNAMICS AFTER CORDECTOMY

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W examined th phonatory function after the removal of one vocal cord. The laryn was X-rayed, vocal cords investigated stroboscopically and recordings of the voice analysed spectrographically and inversely filtered int acoustic glottograms. Subglottic pressure airflow nd sound intensity w re measured with arying phonatory effort.

What happens to the phonatory function, when one vocal cord is removed surgically and what can we attain by phoniatric therapy?

Before treatment the voice is leaky breathy and ineffective. The power of the voice is not proportional to the vocal effort.

After treatment the patient has usually learnt to reduce his vocal effort and the voice has become tighter and stronger The phonation time is longer and the speech sounds clearer Both the patient and the therapist recognize the improvement as a more effective breath control.

Clinical observations indicate that when the cordectomized person increases the sublottic pressure and the glottic air-flow too much, the voice is impaired in quality and force. When he has learnt to reduce the air-flow the function of the glottis improves.

On the basis of this hypothesis we have recorded simultaneously the subglottic lateral pressure the air-flow through the speech apparatus and the voice power Using Schiratzky s method, we inserted a needle connected to an Elema pneumomanometer into the subglottic space. The air flow was measured with a Fleisch pneumotachograph fitted into a face mask. The intensity of the voice was registered with a dynamic microphone connected to the polychannel recorder and with a noise-level meter for direct reading. The pressure is expressed in cm H_2O the air-flow in litre per second, and the voice intensity in dB The calculation of these parameters is greatly facilitated by the fact that during static phonation the flow is one-way and like the pressure, relatively constant.

Fig 1 shows the aerodynamic conditions during phonation of a middle-aged man with a normal voice. At a pressure of 13.2 cm and a mean flow of 0.18 litre the voice reaches an intensity of 74 dB When the subject increases the pressure by 5 cm to 18.2 cm keeping the flow constant — 0.18 litre per second — the intensity of the voice increases by 12 dB to 86 dB. During phonation at low and medium pitch it is only the pressure that changes and varies with the intensity of the voice. The subject was asked to phonate at low pitch for easier comparison with the cordectomized patients voices.

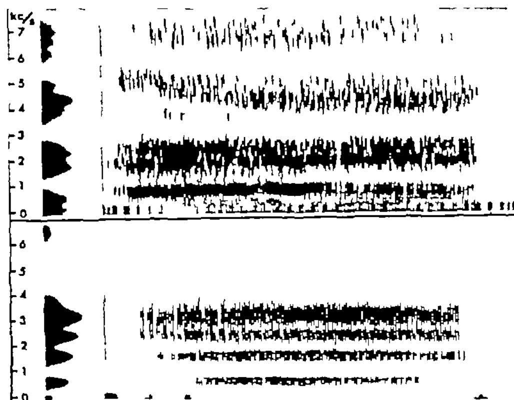


Fig. 4.

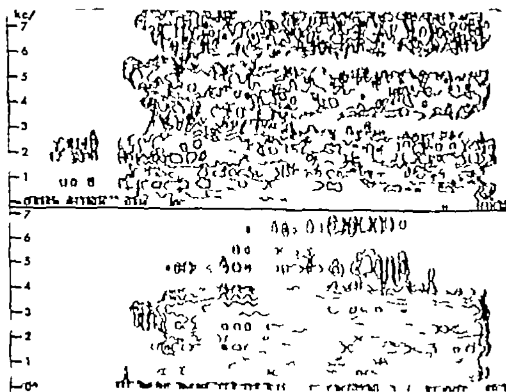
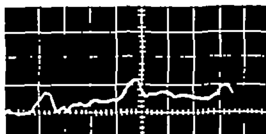
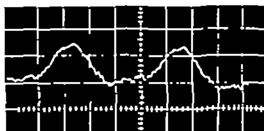


Fig. 5

A



B



C

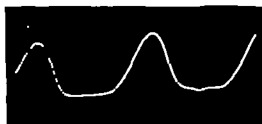


Fig. 6.

tion of the remaining normal vocal cord From 2 000 c/s, the second formant, and upwards, an irregularity begins as in noise. The spectrum seems to be composed of two sound-sources, partly a periodicity from the normal vocal cord, partly a fric tion sound, which gives rise to the hoarseness and which is probably caused by the cord substitute the »excessive» scar tissue formation.

A section analysis of the position and relative energy-content of the formants can be seen in the margin of picture 4. It shows the high frequency of the hoarseness but also that the vocal effort is obviously greater than normal — energy is displaced towards higher frequencies. Such a formant pattern produces uniformity in the different phonemes or speech sounds and diminishes the intelligibility for speech.

A so-called voice print (Fig. 5) consists of iso-amplitudes which encircle areas of the same intensity and shows the spectral irregularities of the voice strength. The normal voice has a less motley pattern than has the cordectomized patient's voice, which looks like a range of hills on a map

At the Speech Transmission Laboratory in Stockholm we have antifiltered the same voice The primary sound that is produced by the vocal cords in their valve-

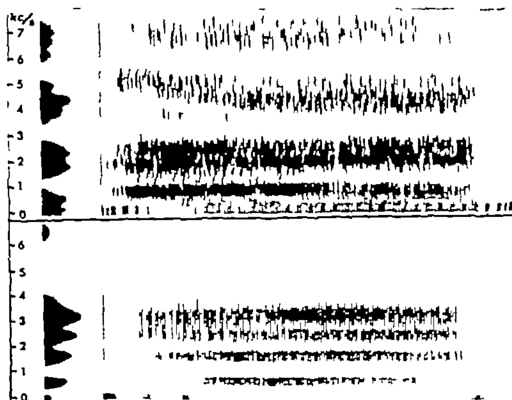


Fig. 4.

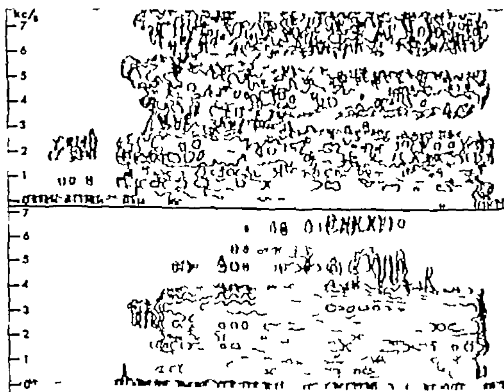


Fig. 5.

DIE STIMMFUNKTION NACH DER BEHANDLUNG VON STIMMBANDKARZINOM IM STADIUM I

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Eine phoniatrische Untersuchung von 38 Patienten, die wegen Stimmbandkarzinom St. I behandelt worden sind.

14 chordektomierte Fälle werden mit 21 primär röntgenbestrahlten Fällen hinsichtlich der Stimmfunktion verglichen. Die röntgenbehandelten Patienten hatten signifikant viel bessere Stimmqualität und signifikant längere Tonhaltedauer, obzwar diese auch bei den letzteren etwas verkürzt war.

Die Chordektomierten wiesen ein kompliziertes Bild von verschiedenerlei Veränderungen im Kehlkopf auf, und der stroboskopische Befund enthüllte bei ihnen fünf verschiedene Arten von Phonationsmechanismus. Die Röntgenbehandelten hatten geringere aber doch unverkennbare Larynxveränderungen.

Auch auf die Notwendigkeit vokaler Rehabilitation wird verwiesen werden.

Die Behandlungsresultate des Larynxkarzinoms sind prozentual immer besser geworden. Beim Stimmbandkarzinom im Stadium I nach der Klassifikation der WHO weisen die 5-Jahresstatistiken oftmals schon über 90 % rezidivfreie Fälle auf, unabhängig davon, ob die Patienten operativ behandelt oder bestrahlt worden sind.

Die Tatsache, dass nach der Behandlung eine gewisse Heiserkeit zurückbleibt, erscheint als eine Bagatelle, wenn man bedenkt, dass die Patienten diese tödliche Krankheit lebend überstanden haben. Gelegentlich werden von der Dysphonie aber Personen betroffen, die in ihrem Beruf weitgehend auf ihre Stimme angewiesen sind. Wenn sie sich dann gezwungen sehen, ihre Arbeit aufzugeben, so bedeutet dies gewöhnlich eine Änderung der persönlichen Lebensumstände mit nicht nur ökonomischen, sondern auch sozialen Folgen. Auch sonst hat der Einzelne im heutigen Gemeinwesen ein psychologisch wohlbegründetes und starkes Bedürfnis nach verbaler Kommunikation. Es erschien uns deshalb gerechtfertigt, eine Nachuntersuchung an derartigen Fällen vorzunehmen, um die Stimmfunktion nach Strahlenbehandlungen einerseits und Chordektomien andererseits zu vergleichen, und um eine Auffassung von der Notwendigkeit phoniatrischer Rehabilitation nach der Behandlung frühen Stimmbandkarzinoms zu gewinnen.

Die meisten Verfasser sind der Ansicht, dass die Stimmfunktion nahezu normal bleibt, wenn das Larynxkarzinom im Stadium I mit Strahlentherapie behandelt wird (Piquet 1958, Evans 1962; Jackson und Norris 1962, Jatho 1963, Taskinen und Holsti 1966).

Wird dagegen eine Chordektomie gemacht, ist das Ergebnis zwar eine schlechtere aber trotzdem oft ziemlich befriedigende Stimme (Piquet 1958, Jackson und Norris 1962; Jatho 1963, Mounier Kuhn u. Mitarb. 1965).

Malbeck und Schlosshauer (1960) untersuchten 40 chordektomierte Patienten nach phoniatrischen Prinzipien. Als durchschnittliches Resultat wurde eine recht brauchbare Stimme erhalten. Die Hälfte der Patienten entwickelten jedoch eine Taschenbandstimme, und vier waren aphonisch geworden (Tabelle 10). Ob die Chordektomie erweitert war oder nicht, stand nach dieser Untersuchung in keinem engeren Zusammenhang mit der Stimmfunktion. In beiden Fällen konnten geringere oder bedeutendere Stimmstörungen aufkommen. In keinem einzigen Falle wurde eine klare Stimme festgestellt. Das entfernte Stimmband wurde freilich erstaunlich gut durch Narbengewebe kompensiert, aber die geschädigte Stimme war nicht viel besser als die gewöhnliche Taschenbandstimme. Infolge der Operation kam es nämlich zu einer Luftleckage in der Glottis, und das neugebildete Narbengewebe hatte meistens kein Schwingungsvermögen. Schliesslich machte die individuelle Narbenbildung die Stimmprognose unberechenbar.

Schönhärls (1960) stroboskopische Zusammenstellung von 700 Fällen enthielt auch 6 chordektomierte Patienten. Alle 6 hatten eine vertiefte, flatternde, überhauchte und rauhe Stimme. Die Hälfte der Behandelten sprachen mit Taschenbandstimme. Bei den restlichen 3 Fällen konnte er feststellen, dass sich anstelle des wegoperierten Stimmbandes ein Schleimhautwulst gebildet hatte. Die operierte Seite erwies sich jedoch sowohl bei der laryngoskopischen wie bei der stroboskopischen Untersuchung als unbeweglich.

Auch Orešković (1965) hat beobachtet, dass die postoperativ entstandene Bandfalte stroboskopisch unbeweglich war. Er hat mit Hilfe seiner stroboskopischen Untersuchungen herausgefunden, dass das nicht operierte Stimmband während der Phonation mit einer horizontalen Komponente gegen das vergrösserte Taschenband der Gegenseite vibrierte. Dieses hinwieder schwang in der Vertikalebene mit weiter Amplitude.

Pfau (1962) hat phoniatrisch die Stimmfunktion bei 57 Patienten untersucht, von denen 40 mit Radium unter Schildknorpelfensterung behandelt worden waren und 9 mit Röntgenbestrahlung. Die erzielte Stimmqualität ist aus Tabelle 10 ersichtlich. Die Behandlung hatte in den meisten Fällen sowohl subjektiv für den Patienten als auch nach der Prüfung der Stimmfunktion eine zufriedenstellende Stimme ergeben. 17 Patienten hatten eine unbefriedigende Stimme, was Läsionen als Folge von Probeexzisionen zur Last gelegt wird. Der Verfasser unterstreicht, dass jeder stärkere Zug am Stimmband zu irreparablen Schäden führt. Klare Stimmen wurden bei 24 Patienten beobachtet, und kein Patient war zum Aphoniker geworden.

EIGENE UNTERSUCHUNGEN

Material

Das Material bestand aus 70 Patienten, die wegen Larynxkarzinom im Stadium I nach der Klassifizierung der WHO behandelt worden waren. Von diesen wurden bei 21 Fälle Thyreotomie und Chordektomie in der Hals- Nasen- und Ohrenklinik der Universität Helsinki gemacht, und die übrigen 49 Fälle bekamen in der Strahlenklinik der gleichen Universität Röntgenbehandlung.

Die Fälle waren in den Jahren 1950—1960 behandelt worden. Mit Rücksicht auf die Observationszeit von 5 Jahren wurden keine später behandelten Fälle mit aufgenommen. Das durchschnittliche Alter der untersuchten Patienten war infolgedessen ziemlich hoch nämlich 63,8 Jahre Daraus erklärt sich z.T., dass nur etwas über die Hälfte sich zur Nachuntersuchung eingefunden hatten.

Die Thyreotomien waren nach der von Meurman (1953) beschriebenen Methode mit rechteckiger Hautplastik durchgeführt worden.

Eine Chordektomie wurde als erweitert angesehen, wenn der Eingriff grösseren Gewebsdefekt verursacht hatte als die gewöhnliche Chordektomie So verhielt es sich in 7 von den untersuchten Fällen. Bei 6 von diesen Operationen war die Mittellinie an der vorderen Kommissur überschritten worden, bei 2 Fällen war ausserdem ein Teil vom Processus vocalis entfernt worden und bei einem Fall ein Stück vom Taschenband auf der gleichen Seite wie der Tumor

Bei der Röntgenbehandlung hatte die von Mustakallio (1944) angegebenen Richtlinien befolgt, es wurden nämlich zwei Felder von 6 × 8 cm Grösse bestrahlt. Die Tumordosis pro Sitzung betrug 215—235 r und die gesamte Herddosis belief sich auf 5 000—5 500 r Die Behandlung nahm gewöhnlich 24 Tage in Anspruch.

Aus Tabelle 1 ist die endgültige Zusammensetzung des Materials ersichtlich.

TABELLE 1

ENDGÜLTIGE ZUSAMMENSETZUNG DES UNTERSUCHTEN MATERIALS

Art der Behandlung	Anzahl der Patienten
Chordektomie	7
Erweitert Chordektomie	7
Röntgenbestrahlung	24
Insgesamt	38

Von den Patienten wurden 4 chordektomierte und 2 mit erweiterter Chordektomie behandelte mit Röntgen nachbestrahlt.

Untersuchungsgang und Methodik

Die Untersuchung gliederte sich folgendermassen. ausführliche Anamnese Palpation der Halsgegend, Inspektion der Mundhohle, vordere und hintere Rhinoskopie und indirekte Laryngoskopie Hierauf folgte die Stimmfunktionsprobe: Bestimmung von mittlerer Sprechstimmlage, Tonhaltedauer Stimmumfang und Stimmregister sowie Vitalkapazität. Die stroboskopische Untersuchung wurde mit Timckes Laryngo-Synchronstroboskop KS 3 vorgenommen Die Lungen wurden von unserem Röntgenologen (C. Sjoblom) untersucht, der auch das frontale Röntgentomogramm vom Kehlkopf bei Atmung und Phonation aufnahm

Es liess sich nicht vermeiden, dass unsere Klassifikation der Stimmen auf subjektiver Beurteilung fusste. Jede Stimme wurde nach Klang, Stärke und Stabilität in eine von der nachstehenden Gruppen zugeordnet.

klare Stimme	Klasse	I
belegte Stimme	»	II
etwas heisere Stimme	»	III
deutlich heisere Stimme	»	IV
sehr heiser oder aphonisch	»	V

Später kontrollierten wir die Einteilung noch mit Hilfe von Tonbandaufnahmen eines Standardtextes, den die Patienten bei der Untersuchung vorgelesen hatten

Ergebnisse

Aus Tabelle 2 ist die Altersverteilung der Patienten ersichtlich Mehr als 4/5 standen im Alter von 61—80 Jahren Das durchschnittliche Alter belief sich auf 63 8 Jahre Erwähnt sei, dass in der Untersuchung von Pfau das mittlere Alter etwas höher war nämlich 65 Jahre

TABELLE 2

ALTER DER NACHUNTERSUCHTEN PATIENTEN IN ZEHNJAHRESGRUPPEN

Zehnjahresgruppe	Anzahl der Patienten
31—40	1
41—50	2
51—60	3
61—70	17
71—80	14
81—90	1
Insgesamt	38

Das Verhältnis zwischen den operierten und den röntgenbestrahlten Patienten war in den verschiedenen Altersgruppen ungefähr gleich

ANAMNESTISCHE ANGABEN

Arbeitsfähigkeit

TABELLE 3

ARBEITSFÄHIGKEIT DER NACHUNTERSUCHTEN NACH CHORDEKTOMIE LAUT [illegible] ANGABE

Behandlung	Pensioniert oder kränklich	Setzten die frühere Tätigkeit fort	Sind zu leichterer Arbeit übergegangen
Chordekt mie	8	2	4
Röntgenbestrahlung	16	7	1
Insgesamt	24	9	5

Wie aus Tabelle 3 hervorgeht, waren 14 von den nachuntersuchten Patienten zur Zeit der Untersuchung arbeitsfähig

Drei Patienten berichteten, sie seien wegen der herabgesetzten Stimmfunktion gezwungen gewesen, ihre frühere Arbeit aufzugeben. Zwei von ihnen waren zu einer leichteren Beschäftigung übergegangen, und der dritte war pensioniert. Drei weitere Patienten betonten dass nach der Behandlung ihre Arbeitsfähigkeit wegen der Dysphonie schwer beeinträchtigt sei. Von diesen 6 Patienten, deren Arbeitsvermögen gemäss eigener Angabe beträchtlich herabgesetzt war waren 5 Chordectomierte, von denen 4 postoperative Röntgenbestrahlung bekommen hatten. Sie hatten deutlich heisere bis aphonische Stimme und wurden zu den Stimmklassen IV oder V gerechnet. In zwei von diesen Fällen wurde mit Hilfe des Stroboskops festgestellt, dass der Phonationsmechanismus ary-epiglottisch war Dieser kommt dadurch zustande, dass der eine oder beide Giessbecken knorpel gegen die hintere Epiglottiswand gedrückt wird, und so eine Stimmritze bildet. In zwei weiteren Fällen wurde die heisere Stimme auf der Höhe des Stimmbandes mit Hilfe eines unregelmässig geformten Narbengewebewulstes gebildet, der an der Stelle des wegoperierten Stimmbandes entstanden war Der sechste von den obengenannten Patienten hatte nur Röntgenbestrahlung bekommen. Seine Stimmqualität wurde als »belegte Stimme« (III) klassifiziert Er war Forst techniker von Beruf und klagte darüber dass er bei kaltem Wetter keine Arbeit mehr im Freien verrichten konnte, und das er keine mündlichen Anweisungen geben konnte ohne heiser zu werden. Die Untersuchung zeigte, dass das rechte Stimmband etwas atrophisch war während das rechte Taschenband im Vergleich zum linken hypertrophisch aussah

Unter den sechs Patienten befand sich auch ein Musiklehrer der gezwungen war seine Beschäftigung als Kapellmeister aufzugeben und sich danach nur noch einem Blasinstrument widmen konnte.

Die einzige Frau unter den Untersuchten war fruher Handlungsgehilfin gewesen, aber auch sie musste ihren Beruf aufgeben und ist nun als Hausfrau tätig

Dysphoniebeschwerden

Mehr als die Hälfte, nämlich 22 von den 38 Nachuntersuchten, war mit ihrer Stimmfunktion unzufrieden.

Von den Röntgenbehandelten war ein Drittel mit ihrer Stimme nicht zufrieden, obwohl sie zur Stimmklasse II gehörten.

Nahezu die Hälfte von den Operierten (6 Patienten) mit deutlich heiserer bis aphonischer Stimme (IV oder V) hatten sich dagegen den neuen Stimmverhält nissen recht gut angepasst und klagten nicht wesentlich über Dysphoniebeschwerden.

Arbeitsfähigkeit und Brauchbarkeit der Stimme aus der Sicht der Patienten

Bei einem Vergleich zwischen der von den Patienten angegebenen Brauchbarkeit der Stimme und ihrer Arbeitsfähigkeit bei der Nachuntersuchung ergab sich folgendes:

Von den 14 Nachuntersuchten, die arbeitsfähig waren, klagten mit Ausnahme von drei alle über Stimmstörungen unterschiedlicher Art. Freilich muss berück

sichtigt werden, dass die Arbeitsfähigen keinen Beruf ausübten, der im allgemeinen grössere Anforderungen an die Stimme stellte. Dies gilt noch weitgehender, wenn man drei von ihnen weglässt, nämlich einen Direktor, einen Kaufmann und einen Forsttechniker. Die übrigen Untersuchten waren in Berufen tätig, wo die verbale Kommunikation weniger Bedeutung hat.

Von den 17 Patienten, die nicht viel über ihre Reststimme klagten, übten nur drei ihren Beruf aus.

Die zur Frage stehenden Patienten waren also grösstenteils mit ihrer Stimmfunktion unzufrieden, und zwar galt dies insbesondere für arbeitsfähige Personen.

ERGEBNISSE DER NACHUNTERSUCHUNG

Stimmqualität

TABELLE 4

STIMMQUALITÄT NACH LARYNXKARZINOM, DAS IN [illegible] IN DEN JAHREN 1950—1960 BEHANDELT WORDEN IST

Behandlung	Anzahl der Patienten	Stimmqualität				
		I	II	III	IV	V
Chordektomie	7	—	—	3	1	3
Erweiterte Chordektomie	7	—	—	—	2	5
Röntgenbestrahlung	24	4	11	7	1	1
Insgesamt	38	4	11	10	4	9

Die röntgenbehandelten Patienten hatten eine weitaus bessere Stimmqualität als die chordektomierten (Tabelle 4), die bei der statistischen Berechnung als eine Gruppe für sich behandelt wurden. Der Unterschied war sehr signifikant (χ^2 = 16.39, $P < 0.001$). Unter den operativ behandelten Fällen waren überhaupt keine Patienten mit klarer (I) oder mit belegter Stimme (II). Bei den Röntgenbehandelten wiederum waren die deutlich heiseren (IV) und die sehr heiseren oder aphonischen Stimme (V) nur mit je einem Fall vertreten. Bei den Fällen jedoch, wo erweiterte Chordektomie angewandt wurde, fehlte sogar die Qualitätsklasse »etwas heiser« (III) gänzlich, und die betreffenden sieben Patienten verteilten sich ausschliesslich auf die Stimmklassen IV und V.

Tonhaltedauer

Die Patienten wurden aufgefordert, möglichst tief Atem zu holen und danach einen Ton mit dem Vokal »o« so lange anzuhalten, wie sie nur konnten. Der Ton war aus der normalen Sprechstimmlage des Patienten gewählt. Die Tonhaltedauer ist normalerweise 15—30 Sek.

Da der Mangel an Vergleichsmaterial ein schwacher Punkt in unserer Untersuchung ist, haben wir diese Lücke behelfsweise dadurch auszugleichen versucht, dass wir das Normalmaterial von Ptacek u. Mitarb. (1966) heranzogen. Die Verfasser untersuchten in Cleveland, USA, eine Gruppe von 31 jungen und eine Gruppe von 27 alten Männern auf deren Stimm- und Atmungsfunktion. Das durchschnittliche Alter in den beiden Gruppen war 27.6 bzw. 76.9 Jahre. Von vorn-

herein waren Personen ausgeschlossen worden, die an Schwerhörigkeit, Asthma Emphysem, Herzinsuffizienz, strukturellen Larynxanomalien und gewissen anderen Zuständen litten, welche die Respiration und Phonation hätten beein flussen können. Unser Vergleich geschieht selbstverständlich unter dem Vorbehalt sowohl methodischer und konstitutioneller als auch milienbedingter Unterschiede in dem untersuchten Material.

TABELLE 5

[illegible]

Behandlung	Tonhaltedauer (sec)				
	n	D	S	t	P
Chordektomie	14	8.14	6.71	2.34	< 0.005
Röntgenbestrahlung	24	13.17	5.75	2.50	< 0.005
Ptacek et al. (1966)	20	18.1	6.6		

D = Durchschnitt S = Standardabweichung

Die Operierten sind bei der statistischen Berechnung in eine Gruppe zusammengefasst (Tabelle 5) In dieser Chordektomiegruppe war die Tonhaltedauer im Vergleich zu den röntgenbehandelten Patienten signifikant kurzer Die letzt genannten wiederum hatten eine signifikant verkurzte Tonhaltedauer im Vergleich zu der getriatrischen Normalgruppe in der Untersuchung von Ptacek u Mitarb

Die besonders in der Chordektomiegruppe verschlechterten Werte beruhen u.E nach in erster Linie darauf dass die Phonation einen abnorm grossen Luft verbrauch in der Glottis erfordert. Die Patienten mit erweiterter Chordektomie bei denen die Gewebedefekte grösser waren als bei der gewohnlichen Chordektomie wiesen die zahlenmassig grossten Luftleckagen auf, aber der Unterschied war nicht signifikant.

Es moge hier auf Döhne (1944) verwiesen werden, nach welchem Patienten mit schwerer Dysphonie bei der Phonation 4—5 mal so viel Luft verbrauchen wie normalerweise Arnold (1958, 1965) drückt den Sachverhalt so aus, dass die Tonhaltedauer gewohnlich umgekehrt proportional zum Grad der Heiserkeit bei paralytischen Dysphonien ist. Aber nach ihm herrschen auch die gleichen aero-

TABELLE 6

[illegible] MATERIAL

Behandlung	Vitalkapazitat (ml)				
	n	D	S	t	P
Chordektomie	14	3707	1016	0.19	> 0,005
Röntgenbestrahlung	24	3774	1031	2.54	< 0.05
Ptacek et al. (1966)	27	3100	700		

dynamischen Prinzipien bei anderen organischen Zuständen wo der Verschluss der Stimmritze lückenhaft ist vorligt z.B nach Chordektomie

Bei der statistischen Behandlung der Messungsergebnisse betreffs Vitalkapazität (Tabelle 6) liess sich kein signifikanter Unterschied zwischen operierten und röntgenbehandelten Patienten feststellen. Etwas erstaunlich ist es dagegen, dass alte Leute in *Ptaceks Material* im *Vergleich zu unseren Gruppen* eine signifikant niedrigere Vitalkapazität hatten Abgesehen von schwer erfassbaren methodischen und konstitutionellen Unterschieden muss jedoch darauf hingewiesen werden, dass das mittlere Alter in unserem Material 13 1 Jahre niedriger war Auf die Tonhaltedauer hat dies jedoch keinen Einfluss gehabt, das zeigt Tabelle 5 Es ist nicht unmöglich dass die Luftleckage bei der Phonation in unseren Fällen eine Stimulanzwirkung auf die Atemfunktion ausgeübt hat, derzufolge der Involutionsprozess verzögert wurde.

Stimmumfang

Die Stimme hat normalerweise einen physiologischen Umfang von 2—3 Oktaven Hierzu wird die gesamte Tonskala gerechnet, vom tiefsten Brummen bis zum höchsten Fistelton den der Patient noch hervorzubringen vermag Bei älteren Personen muss man mit einer grösseren oder geringeren Einschränkung rechnen In Ptaceks geriatrischem Material belief sich der physiologische Stimmumfang auf etwas über zwei Oktaven Dieser Mittelwert weicht sehr signifikant von dem entsprechenden Mittelwert in der Gruppe der jungen Männer ab

TABELLE 7

STIMMUMFANG DER NACHUNTERSUCHTEN EINGETEILT IN DREI VERSCHIEDENE KATEGORIEN UND VERTEILUNG AUF DIESELBEN IN BEZIEHUNG ZUR BEHANDLUNGSWEISE

Stimmumfang	Behandlung und Anzahl der Patienten		
	Chordektomie	Erw Chordektomie	Röntgen
< eine Oktave	3	1	3
> eine Oktave	4	5	16
> zwei Oktaven	—	1	3

Etwas über ¼ von den operierten Patienten hatten einen geringeren Stimmumfang als eine Oktave, während nur 1/8 von den Röntgenbehandelten einen so kleinen Stimmumfang hatten (Tabelle 7) Dieser Unterschied war statistisch jedoch nicht signifikant.

Stroboskopische Untersuchungen

Da das Schliessungsvermögen der Glottis ein ausschlaggebender Faktor für den Klang der Stimme ist, haben wir dies in Tabelle 9 durch Einteilung einiger wichtiger stroboskopischer Charakteristika zugrunde gelegt.

Keiner von den chordektomierten Patienten wies einen guten Stimmritzenverschluss auf Bei den nur mit Röntgen Behandelten war der Stimmritzenschluss in 11 Fällen ungenügend, während 13 von den Nachuntersuchten einen nahezu normalen Stimmritzenschluss hatten.

Ein guter Glottisschluss ist jedoch keine Garantie für eine klare Stimme. Bei den drei Untersuchten, die beiderseits normale Stimmbandschwingungen aufwiesen, hatten die Stimmbänder rauhe Ränder, was u.E. nach die Ursache für ihre belegte oder etwas heisere Stimme war. Ihre Stimmen waren zur II., II und III Klasse gerechnet worden.

Die unilateral reduzierten Schwingungen befanden sich in 9 von den 10 röntgenbehandelten Fällen auf der Seite, wo das Karzinom ursprünglich diagnostiziert worden war.

Der eine Fall mit unilateral reduzierten Schwingungen war mit Chordektomie behandelt worden. Die Schwingungen wurden auf einen Bindegewebewulst lokalisiert, der sich an der Stelle des wegoperierten Stimmbandes gebildet hatte. Das andere Stimmband vibrierte mit weiter Amplitude. (Siehe unten im Anschluss an Tabelle 8.)

In den drei Fällen, wo stroboskopisch ein Stimmbandstillstand festgestellt wurde und die mit erweiterter Chordektomie behandelt worden waren, handelte es sich ebenfalls um einen Bindegewebewulst postoperativen Ursprungs. Das andere Stimmband wies gleichzeitig regelmässige aber auch unregelmässige Schwingungen auf.

TABELLE 8

STROBOSKOPISCHE CHARAKTERISTIKA BEI UNGENÜGENDEM UND GUTEM STIMMRITZENSCHLUSS BEI 37 NACHUNTERSUCHTEN PATIENTEN

Stroboskopiebefund	Stimmritzenschluss					
	ungenügend			gut		
	Che	EChe	Rtg	Che	EChe	Rtg
Normale Stimmbandschwing. bilateral	—	—	—	—	—	3
Unilat. reduzierte Stimmbandschwingungen	1	—	5	—	—	5
Unregelm. bilaterale Schwingungen	—	—	4	—	—	4
Stroboskopisch Stimmbandstillstand	—	3	1	—	—	1
Aryepiglottische Schwingungen	4	1	—	—	—	—
Taschenbandschwingungen bilateral	—	2	1	—	—	—
Taschenbandschwingungen unilateral	1	—	—	—	—	—
Taschenband-aryepiglottische Schwingungen	1	—	—	—	—	—
Insgesamt	7	6	11	—	—	13

Che = Chordektomie
EChe = erweiterte Chordektomie
Rtg = Röntgenbestrahlung
Ein primär röntgenbehandelter Patient konnte nicht stroboskopiert werden, weil er aphonisch war.

Ary-epiglottische Schwingungen findet man vereinzelt bei einem Stimmechanismus, wo eine Pseudoglottis am zusammengepressten Kehlkopfeingang entsteht. Beck und Schönhärl (1959) hat zwei derartige Fälle beschrieben und dabei vier ähnliche aus der Literatur erwähnt. Malbeck und Schlosshauer hatten ebenfalls auf 2 Fälle in ihrem Material hingewiesen.

Die Stroboskopie hatte ausschlaggebende Bedeutung für die Ermittelung des Phonationsmechanismus. Die Tonquelle dagegen konnte direkt bestimmt werden, indem die vibrierenden Schleimhautpartien im Kehlkopf lokalisiert wurden. Bei

TABELLE 9

DIE STIMMQUALITÄT DER CHORDEKTOMIERTEN PATIENTEN IN BEZIEHUNG ZUM PHONATIONSMECHANISMUS

Phonationsmechanismus	Anzahl der Patienten	Stimmqualität				
		I	II	III	IV	V
Ary-epiglottische Stimme	5	—	—	1	1	3
Hemistimmbandstimme	4	—	—	1	1	2
Taschenbandstimme	3	—	—	—	1	2
Stimmband Taschenbandstimme	1	—	—	1	—	—
Ary Taschenbandstimme	1	—	—	—	—	1
Insgesamt	14					

schwerer Dysphonie waren wir gezwungen, die Tongeneratorsteuerung des Stroboskops zur Hilfe zu nehmen.

In Tabelle 9 sind die 5 Arten von Phonationsmechanismus zusammengestellt, welche nur bei den chordektomierten Patienten unterschieden werden konnten

Beim ary-epiglottischen Stimmemechanismus wurde der Kehlkopfeingang zusammengepresst, und die Schleimhaut der einen oder beider Giessbeckenknorpelpartien vibrierte gegen einen Wulst auf der dorsalen Seite der Glottis. In einem Falle wurden die Schwingungen auf die eine Ary-epiglottisfalte lokalisiert. Auf diese Weise kam eine Pseudoglottis zustande die ungefähr rechtwinklig zur normalen gestellt war

Bei zwei von den fünf Patienten mit ary-epiglottischer Stimme war die Beweglichkeit des angegriffenen Stimmbandes schon vor der Operation herabgesetzt. Bei *einen von diesen zwei Fällen war es ganz unbeweglich und ausserdem fehlte* das homolaterale Taschenband Bei den übrigen zwei Fällen konnten wir eine Recurrensparese bei der Nachuntersuchung feststellen Im fünften Falle war uns das zustande kommen des Mechanismus unerklärlich Man kann vielleicht den ary-epiglottischen Stimmechanismus so verstehen, dass der Patient die Kehle auf demjenigen Niveau zusammenpresst oder schnürt, wo es am besten geht. Die Möglichkeiten für stimmbandähnliche Schleimhautschwingungen sind aber hier deutlich schlechter als auf dem Niveau des Taschenbandes.

Nach der Chordektomie bildet sich nicht selten einen Bindegewebewulst an der Stelle des entfernten Stimmbandes. Manchmal hat dieser Wulst die gleiche Ausdehnung und auch eine ähnliche Form wie ein normales Stimmband. Bei unseren 14 Nachuntersuchten wurden 5 derartige Wulste gefunden von denen drei nach erweiterter Chordektomie entstanden waren. In 4 Fällen konnte stroboskopisch nachgewiesen werden dass dieser Gebilde das intakte Stimmband stützten und dadurch an der Phonation teilnahmen. Dies ist ein Stimmechanismus, der in unseren 4 Fallen eine heisere bis aphonische Stimme (III V) ergab. In Tabelle 9 haben wir sie als Hemistimmbandstimme bezeichnet.

In 4 von den 5 Fällen war der postoperativ entstandene Wulst unbeweglich, im fünften Falle beweglich (Abb 1).

Die verschiedenen Grade von Dysphonie verteilen sich ungefähr im gleichen Verhältnis auf die drei gewöhnlichsten Stimmechanismen der Tabelle. Die zwei

restlichen könnte man vielleicht als Streufälle betrachten, aber die Kleinheit des Materials erlaubt leider keine Schlussfolgerungen.

Die primär röntgenbestrahlten Patienten sprachen alle mit Stimmbandstimme bis auf einen, der eine aphonische Taschenbandstimme hatte. Dieser Patient hatte fünf direkte Laryngoskopien durchgemacht, war kränklich und trank ziemlich viel.

Besprechung der Ergebnisse

In Tabelle 10 sind die Resultate von früheren Untersuchungen über die Stimmqualität der Patienten nach Behandlung von Larynxkarzinom St. I wiedergegeben. Anderes Material, wo die resultierende Stimmfunktion bei chordektomierten und strahlenbehandelten Fällen verglichen wurde, haben wir nicht ausfindig machen können. Wir hoffen daher, dass die vorliegende Untersuchung trotz ihres knappen Materials nicht ohne Interesse ist.

TABELLE 10

ZUSAMMENSTELLUNG DER STIMMQUALITÄTEN NACH LARYNXKARZINOM ST. I GEMÄSS VERSCHIEDENER SCHÄTZUNGSWEISER BEURTEILUNG SOWIE IN BEZIEHUNG ZUR BEHANDLUNGSWEISE

Autoren	Behandlung	Anzahl der Patienten	Stimmqualität I	II	III	IV	V
Malbeck und Schlosshauer 1960	Che	10	4	2	3	1	
	EChe	30	15	5	7	3	
Taskinen und Holsti 1966	Rtg	30	16	11	3	—	
			I	II	III	IV	V
Pfau 1962	Rad 48, Rtg 9	57	21	4	12	11	6
Riska und Lauerma 1967	Che	7	—	—	3	1	3
	EChe	7	—	—	—	2	5
	Rtg	24	4	11	7	1	1

Che = Chordektomie Rad = Radiumbestrahlung
EChe = erweiterte Chordektomie Rtg = Röntgenbestrahlung

Zu bemerken ist, dass in den Materialien, wo die Stimmqualität in vier Klassen eingeteilt ist, die Bezeichnung I eine »gute« Stimme bedeutet, in den zwei restlichen dagegen, wo die Einteilung fünf Klassen umfasst, damit eine »klare« Stimme gemeint ist. Es muss zugegeben werden, dass eine solche Einteilung aufgrund von subjektiven Kriterien prinzipiell eine methodische Schwäche bedeutet. Da aber die ganze Skala der Stimmqualitäten ziemlich gleichmässig repräsentiert ist, und die Beurteilung der Reihe nach gemacht wurde, glauben wir, der Wirklichkeit doch ziemlich nahe zu kommen.

In der Arbeit von Malbeck und Schlosshauer hatte nur gut ein Drittel von den Patienten heisere Stimme. Die Hälfte von diesen Patienten waren Taschenbandsprecher, 4 waren aphonisch geworden, und keiner hatte eine klare Stimme nach der Operation.

Unsere Chordektomierten waren ausnahmslos heiser und in den Fällen mit erweiterter Chordektomie war nicht einmal die Klasse »etwas heiser« (III) vertreten. Vier Patienten waren Aphoniker geworden.

nach der Behandlung oder (5) auf der Stimmfunktion des Patienten vor während oder nach der Röntgenbehandlung beruhen

Zur Zeit der Nachuntersuchung hatten nur einige Patienten Stimmübungsbehandlung bekommen

Manche Verfasser sind geneigt, die Reststimme die dem Patienten nach der Behandlung dieser frühen Stimmbandkarzinome zur Verfügung steht zu überschätzen Die Stimme und ihre Rehabilitation verdienen im allgemeinen weit mehr Aufmerksamkeit als bisher der Fall gewesen ist. Es genügt nicht dass das Leben des Patienten und der Kehlkopf gerettet wird. Oftmals bleibt eine betrachtliche Heiserkeit zurück, die phoniatrische Untersuchung und Behandlung erfordert ehe der Patient wieder seinen Beruf aufnehmen und sich der Umwelt störungsfrei anpassen kann Optimale Stimmfunktion bedeutet ein Minimum mechanischer Beanspruchung für Stimmband und Kehlkopf und dann ist auch die gefährdete Larynxschleimhaut am besten vor Infektionen und Noxen geschützt. Unter sachkundiger Leitung lernt der Patient am besten und schnellsten die ihm verbliebene Reststimme auszunutzen

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MUCUS FLOW IN THE SUBGLOTTIC REGION STUDIED BY TRANSCONIOSCOPY

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A new method for observing the mucus flow in the human subglottic region is described and the different flow patterns under normal and pathologic conditions are discussed.

The material is still too small for definite conclusions, but the method may become a diagnostic aid in evaluating the extension of pathologic lesions and the type of treatment to be choosen.

Mucus flow in the respiratory tract pre-requisites, ia, a ciliated epithelium. With the exception of a 2 to 4 mm wide area along the free edges of the vocal cords which is covered by a nonciliated squamous epithelium, the laryngeal and tracheal mucosa is lined by a ciliated columnar epithelium of the respiratory type (Jelinek, 1966)

Animal studies have shown that the mucus flow propelled by the tracheal cilia mainly follows the long axis of the trachea in a cranial direction. In the subglottic region, however the stream turns posteriorly when meeting the non-ciliated layer and runs parallel to the vocal cords towards the interarytenoid fold (Hilding 1950).

Human studies of the subglottic mucus flow have not been reported, but the introduction of transconioscopy (Mårtensson, et al 1964) has facilitated these studies and for some time an investigation has been going on at the Department of Otolaryngology Karolinska sjukhuset, with the aim of observing the different flow patterns in patients with laryngeal disorders.

Methods

For a detailed description of transconioscopy see Mårtensson et al. 1964

As transconioscopy is carried out under local anaesthesia it is important that the drugs used do not at least to any greater extent, affect the mucus flow by changing the ciliary beat rate or the viscosity of the secretions. Atropine is known to have a drying effect, and must therefore not be used for premedication. In a special study (Ewert, 1967) Xylocaine (Lidocaine) 4 per cent has been found not to affect the mucus flow and has consequently been used in the present study for topical anaesthesia of the larynx by injection through the cricothyreoid membrane

By direct observation through the transconioscope the flow of the mucus can be followed by observing the small air bubbles entrapped in the secretions, or by blowing a tracer powder[1]) through the casing of the scope into the subglottic region

[1]) Dibasic calcium phosphate 97 per cent and Edicol Supra Orange ICI, 3 per cent.

Material

The present material consists of 20 patients, 14 of which had carcinoma of the larynx and the others benign tumours or chronic laryngitis. Some of the tumour cases had only supraglottic growth and some were strictly unilateral. The healthy regions were used as controls, as there are no normal subjects included in this series. Histologic studies of biopsies, vocal cord excisions and laryngectomies have been correlated to the preoperative flow patterns in some of the cases.

Results

The normally found flow pattern in the human subglottic region as observed from the present control material, seems to be identical to the one found by Hilding in his animal studies. Fig 1 is a synthesis of the present control findings,

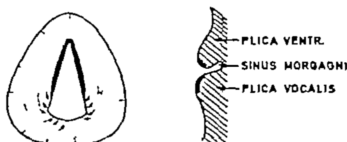


Fig. 1 Synthesis of the mucus flow pattern in the normal subglottic area as seen by transcoleoscopy. \ nciliated squamous epithelium (found at the heavily marked areas on the true and false cords.

demonstrating the anterior portion of the tracheal mucus stream splitting into two at the anterior commissure and passing very close and parallel to the free edges of the vocal cords to the arytenoid region, where the stream resumes its upward path, mingling with the posterior portion. The flow rate is relatively high, 10 to 15 mm per minute while tracer powder blown into the free edges of the cords remain stagnant for many minutes, thus demonstrating a clearly visible, sharp line of demarcation a few mm below the free edges. Biopsies have shown this line to be identical to the one between ciliated and non-ciliated epithelium.

In the unilateral tumour cases a typical asymmetric pattern has been found. On the healthy side the flow is the same as the one just described while on the

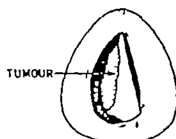


Fig. 2 Typical asymmetric flow pattern around a carcinoma of the vocal cord.

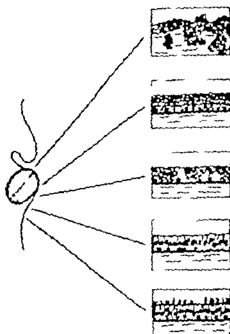


Fig. 3. Schematic drawing of the gradual changes of the epithelium from normal ciliated (bottom) t true carcinoma (top).

tumour side no flow could be detected over an apparently normal mucosa some 5 to 15 mm below the visible tumour (fig. 2). The histological study of such a case is shown schematically in fig 3 demonstrating the gradual steps of metaplasia from the normal ciliated epithelium to the true carcinoma. The disappearance of cilia seems to be the very first sign of change and this in turn results in stagnation of the mucus stream.

The histologic observations and the preoperative flow patterns are in full accordance in the present material, which means that mucus flow is only possible over a normal epithelium and that stagnation of mucus possibly indicates some sort of metaplasia

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ON THE MECHANICS OF THE EXTRATHORACIC AIRWAYS

A PRELIMINARY REPORT[1]

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For adequat treatment it is important t distinguish between organic tenosis and increased compressibility of the extrathoracic airways. A diagnostic method that may help in this distinction, is presented. I this method the patient is breathing through a volume flow regulator which permit only a know consta t flow The resistance of the xtrath racic airways d the mouth pressure are measured sim ltaneously at different levels of mouth pressure The combination f compressive forces and loss of normal rigidity may in some cases ca se a inspiratory collapse f the extrathoracic airw y — This phenomenon — dynamic compression — may sometimes be a dominant factor in increasing extrathoracic airw y resistance

Laryngeal and tracheal disease or trauma often cause a narrowing of these air ways This narrowing may be due to two principally different conditions. First the lumen may be more or less occluded by tissue growing into dislocated into or *compressing the lumen* This is called *organic stenosis. This concept includes* fenomena like oedema and bilateral adductor paralysis. Second the normal rigid ity of the extrathoracic airways may be lost resulting in transient compression of the lumen by *forces acting on the walls of these airways. This is called dynamic* compression

The outside of the extrathoracic airways is subjected to a pressure which probably is approximately atmospheric and constant The pressure acting on the inside of the airways, that is the lateral pressure of the gas, differs from atmospheric for two reasons.

1) The resistance from airway opening i e the mouth to a certain point in the airways causes a pressure increase at that point during expiration and a pressure decrease during inspiration
2) The acceleration of the gas causes a decrease of the lateral pressure at that point both during inspiration and expiration This is called Bernouilli effect

Under most conditions the lateral pressure within the extrathoracic airways is higher than atmospheric during expiration Thus these airways tend to be expanded during expiration During inspiration the lateral pressure is always less than atmospheric within the extrathoracic airways. *Thus these airways tend to be compressed* during inspiration. This is called dynamic compression of the extrathoracic airways The degree of compression depends on 1) the compressive pressure 2) the compressibility of the airway

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[1]) This investigation w supported by gra t from The Swedi h N tio l A soci tion gainst Chest and H art Disease

The compressive pressure increases with increasing flow rate with increasing resistance from airway opening to the studied point and with decreasing lumen at that point. Thus the compressive pressure increase in cases with stenosis in the extrathoracic airways and very much so

If the normal rigidity of the extrathoracic airways is lost the compressive pressure may lead to a pronounced dynamic compression This gives a reduction of the lumen and an increase of the resistance with further promotes the compressive pressure: a viscious circle is started

From the discussion above it is clear that surgical therapy must in some cases aim at removing the organic stenosis, in others at stabilizing the wall of trachea or larynx In some cases both of these procedures must be performed The diagnostic procedure must therefore tell how much organic stenosis and how much increased compressibility contribute to the respiratory distress of the patient

The method used until now for determination of the extrathoracic airway resistance was first published by Hoorn and Ingelstedt (1960), by Hyatt and Wilcox (1960), and by Ferris, Mead and Opie (1960) and has later been used by Schiratzky (1963) and others. In this method the pressure difference between mouth and trachea is measured simultaneously with volume flow at the mouth ($\dot{V}$)

The method presented here includes the same measurements. However the flow measurement is merely used to controle the function of a volume flow regulator (VFR) a valve that keeps the volume flow rate at a constant known value (fig. 1) The flow rate is thus constant regardless of the effort of the subject The pressure in the mouth, relative to atmospheric (Pm), is, however affected by effort.

A great inspiratory effort gives a pronounced negative Pm, a great expiratory effort gives highly positive Pm. The compressive pressure is of course affected by Pm Thus in our method the resistance of the upper airway Ruaw (cmH_2O/LPS) may be studied at a constant flow rate independent of effort while the compres-

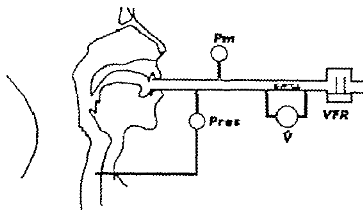


Fig. 1 Experimental setup The resistance Ruaw is calculated from the resistive pressure Pres, and the volume flow $\dot{V}$ according to the formula Ruaw = Pres/$\dot{V}$. The volume flow is fixed by a volume flow regulator VFR. Pm = mouth pressure.

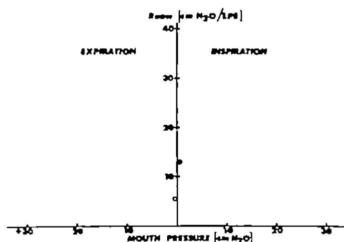


Fig. 2. Data from a patient with tracheomalacia caused by repeated tracheostomies. The inspiratory resistance increases markedly with increasing negative mouth pressure

sive pressure changes with effort The change in compressive pressure is estimated by Pm

Results from normal adults show that Ruaw is unaffected by Pm which means that the degree of dynamic compression is too small to cause a significant increase in resistance. The same is true for small children as shown by Ingelstedt, Jonson and Tibbling (1966) This was also to be expected as in normal man the compressive pressure and the compressibility of the extrathoracic airways are small.

In cases with lost rigidity of the extrathoracic airways (fig 2) the expiratory resistance is low The inspiratory resistance is high and increases with increasing negative mouth pressure. This is explained by an increased compressibility of the extrathoracic airway leading to a pronounced dynamic compression

In cases with an organic stenosis the expiratory resistance is high. The inspiratory resistance is also high and may increase with increasing mouth pressure because even a moderate decrease in the lumen of an already narrow tube leads to a great increase in resistance

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ZUM PROBLEM DES RAUCHERKEHLKOPFS

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Nach einem kurzen Überblick über die Anfänge der Untersuchungen zum Problem des Raucherkehlkopfs haben wir uns mit den möglichen Wirkungsmechanismen des Tabakrauchs auf den Kehlkopf auseinandergesetzt. Als Gegenstand unserer Untersuchungen dienten uns 597 larynxkrank. Patienten der Grazer Universitäts Hals-Nasen-Ohren-Klinik aus den Jahren 1960—1965 und 35 Leichenkehlköpf. Es wurden klinische und pathohistologische Untersuchungen angestellt um den Begriff des Raucherkehlkopfs näher zu beschreiben. Im klinischen Bild und in der Pathohistologie bestehen nur graduelle und keine prinzipiellen Unterschied zu Larynxveränderungen anderer Ätiologie. Zwischen dem Raucherkehlkopf und dem Kehlkopfkrebs fanden wir nur mittelbare Zusammenhänge.

Es hat in keiner Zeit an Warnern vor der Schädlichkeit des Tabakrauchens gefehlt. Selbst Könige wie Jakob I. von England, sahen sich veranlasst, Streitschriften gegen das Tabakrauchen herauszugeben. Nicht einmal Verbote aber konnten verhindern, dass sich der Tabakgenuss über ganz Europa sehr rasch nach seiner Einführung ausgebreitet hat und heute sicher in allen seinen Formen zu einem der beliebtesten Genussmittel zählt. Ärzte wie. v. Praag (1855) Gibb (1860) und Swain (1904) haben sowohl experimentell im Tierversuch und an Hand klinischer Untersuchungen am tabakrauchenden Menschen versucht u.a. die Veränderungen des Kehlkopfs nachzuweisen. Einzig Lack (1905) hat die Behauptung aufgestellt, dass der Tabakrauch keinerlei Auswirkung auf den Kehlkopf habe. Gerade in letzter Zeit mehren sich Abhandlungen über den Raucherkehlkopf. Nach Ansicht vornehmlich amerikanischer Autoren wie Meyerson (1950) Wallner (1954, 1957) und Ryan et al. (1955) erscheint dieser als festumrissener klinischer Begriff der immer mehr in den Blickpunkt des medizinischen Interesses rückt. Dies nicht zuletzt deshalb da der Tabakrauch stets mit der Ätiologie des Kehlkopfkrebses in Zusammenhang gebracht wird.

Wichtige Bestandteile des Tabakrauchs.

1. Nikotin und Derivate
2. Pyridin und Pyridinbasen
3. Amine und Ammoniak
4. Blausäure und Rhodan
5. Schwefelwasserstoff
6. Kohlenmonoxyd und Kohlendioxyd
7. Organische Säuren
8. Tabakharze
9. Tabakteer und Kohlenwasserstoffe
10. Wasser

Die im Tabakrauch enthaltenen Substanzen wirken in dreierlei Weise auf den Kehlkopf ein

1 Lokale Wirkung im Sinne der Schleimhautreizung durch die Tabakrauchbestandteile wie Nikotin Pyridin Amine Ammoniak aber auch hervorgerufen durch organische Säuren und Schwefelwasserstoff Folge dieser langanhaltenden Reizung ist die chronische Entzündung des Kehlkopfes, die von allen Autoren in ihren Abhandlungen über den Raucherkehlkopf angeführt wird

2. Die Nikotinwirkung durch Beeinflussung des vegetativen Nervensystems im Allgemeinen ist offenbar nicht sehr wesentlich Nach Angaben von Schnedorf und Ivy (1939) ist die durch einige Zigaretten zugeführte Alkaloidmenge viel zu gering um die Speichelsekretion entscheidend zu beeinflussen Daneben ist nach Burgen und Emmelin (1961) noch die Nikotintoleranz des gewohnheitsmässigen Tabakrauchers zu berücksichtigen. Trotzdem erschien uns die Phase der Einschränkung der glandulären Sekretion bei der Laryngitis des Rauchers verlängert zu sein

3 Kanzerogene Wirkung durch die im Tabakteer enthaltenen aromatischen Kohlenwasserstoffe Die anfallenden Mengen cancerogener Substanz sind jedoch sehr gering sodass Autoren wie Proetz (1939) Hilding (1956) und Blümlein (1957) Hilfsmechanismen anführen. Diese sind Abriss des Flimmerstroms auf metaplastischen Epithelinseln und feinsten Epithelläsionen beides im Rahmen der chronischen Entzündung oft zu beobachten. Daneben soll durch Wirbelbildung erzeugte Tabakteersedimentation eine Rolle spielen All das führt zum innigen Kontakt der Kohlenwasserstoffe mit geschädigter oder verletzter Schleimhaut. Untersuchungen von Blümlein (1957) haben zeigen können dass neben dem Rauchen besonders die berufliche Inhalationsnoxe und am ehesten eine Kombination beider Wegbereiter des Kehlkopfkrebses sein können

Untersuchungsgut und Untersuchungsmethoden

Grundlage für unsere Untersuchungen bildete das Patientenmaterial der Grazer Universitäts-Hals-Nasen-Ohrenklinik aus den Jahren 1960—1965 Wir haben alle Patienten mit Kehlkopfaffektionen, insgesamt 597 die bei uns in Behandlung gestanden sind, nach folgenden Gesichtspunkten aufgegliedert.

1 Trennung der Patienten in Raucher und Nichtraucher wobei wir bewusst davon Abstand genommen haben in starke und schwache Raucher zu unterteilen Dies nicht zuletzt deshalb da Fragen nach der Zahl der gerauchten Zigaretten sowie nach der bevorzugten Sorte meistens ausweichend und unrichtig beantwortet werden Von einem Raucher haben wir gesprochen wenn er mindestens 10 Zigaretten pro Tag geraucht hatte und das ständig durch Jahre.

2. Aufteilung der Patienten in Altersgruppen und nach dem Geschlecht.

3 Trennung der Patienten in Berufsgruppen mit und ohne Kehlkopfbelastung

4 Gegenüberstellung der Patientengruppen mit gut und bösartigen Kehlkopferkrankungen

Ein anderer Teil unserer Untersuchungen befasste sich mit der Sichtung aller aus den Kehlkopfen unseres Patientenmaterials entnommenen Probeexcisionen.

Dies sollte uns helfen, klinische Diagnosen histologisch zu verifizieren und praecanceröse Veränderungen auf ihren Malignitätsgrad zu prüfen.

Um nun den von uns gefundenen Zahlen eine Aussagekraft zuerkennen zu können haben wir im Sinne der Ereignisstatistik auf Signifikanz geprüft. Es besteht Signifikanz, wenn 3S grösser als pp., wobei pp die Differenz der relativen Haufigkeiten darstellt Das Sigma berechneten wir nach dem strengen Differenzenverfahren

Der letzte Teil unserer Untersuchungen befasste sich mit der histologischen Prüfung von 30 Leichenkehlköpfen. Diese stammten von Rauchern nach der vorher angeführten Definition aus den Altersgruppen 40—60 Jahre Damit wollten wir von vornherein einer längeren Exposition Rechnung tragen. Klinisch waren die Verstorbenen zum Zeitpunkt des Todes kehlkopfgesund. Nach Fixierung des Kehlkopfs in neutralem Formol haben wir Stimmband Ventrikel und Taschenband jeder Seite im Block ausgelöst und nach Paraffineinbettung in Stufenserie geschnitten. Wir bedienten uns konventioneller Färbemethoden wie Hämatoxilin Eosin, Weigert van Gieson und der PAS-Reaktion nach Mac Manus Unser besonderes Interesse galt

1 Dem Verhalten des Epithels an Stimm- und Taschenband.
2. Entzündungszeichen in der Submucosa
3 Dem Bild der Drüsen im Ventriculus laryngis
4 Subepithelialer Ödembildung insbesondere am Stimmband.

Da die von uns untersuchten Kehlköpfe von Nichtrauchern, es waren nur fünf keinerlei schlüssige bzw signifikante Vergleiche in Folge des Fehlers der kleinen Zahl zulassen, sind unsere erhobenen Befunde nur als Beobachtung zu werten Sie sind bedingt vergleichbar mit den von Ruckes (1961) erhobenen Befunden der das Bild der Dyschylie und mit Causé (1961) zusammen das Verhalten des Epithels an 150 Leichenkehlköpfen untersucht hat.

Untersuchungsergebnisse

1 *Klinische Daten*

In der Tabelle 1 sind 317 untersuchte Patienten entsprechend ihrer Berufsgruppe angeführt. 4 ,3 der Larynxkranken gehen einem Beruf mit Kehlkopf belastung nach In dieser Gruppe stehen 89 Raucher nur 61 Nichtrauchern gegen

TABELLE 1

[illegible]

	Raucher	Nichtraucher	Gesamt
Metallarbeiter	32	21	53 16
Bergbau und Bauarbeiter	14	16	30 9 5
Chemiearbeiter	18	10	28 8 8
Sprechberuf	25	14	39 = 12 3
Sonstige Beruf	51	116	16 5
Berufe mit Kehlkopfbelastung		61 = 40 7	150 4 3
Beruf ohne Kehlkopfbelastung		116 = 69.5	167 52

über während in der Gruppe der Patienten ohne Kehlkopfbelastung nur 51 Raucher 110 Nichtraucher aber aufscheinen. Dies heisst, dass Patienten mit Kehlkopferkrankungen neben einer beruflichen Kehlkopfschädigung noch zusätzlich in der Mehrzahl eine Inhalationsnoxe durch den Tabakrauch erleiden.

In der Tabelle 2 sind nach Altersgruppen aufgeschlüsselt 185 von uns untersuchte larynxkranke Männer enthalten Von diesen waren 56% = 101 Raucher Der hohe Prozentsatz der Raucher schon in der ersten Altersgruppe lässt die Expositionszeit als wesentlichen Faktor bei der Entstehung des Raucherkehlkops in den Hintergrund treten. Vergleichweise sind in dieser Tabelle auch 262 Larynxcarcinomträger angeführt von denen nur 42.1% = 111 Raucher gewesen sind

TABELLE 2
LARYNXKRANKE MÄNNER 1960—1965

Altersgruppen	davon Raucher		
0—20	17	0	
20—30	20	10	50.0%
30—40	18	20	41
40—50	32	17	53.1%
50—60	48	31	70.8%
60—70	29	19	65.5%
über 70	8	4	50.0
über 20	185	101	56.0%
Larynxcarcinome	262	111	42.1%

Die Tabelle 3 enthält unter denselben Gesichtspunkten angeführt unser weibliches Patientengut. Nur 27.2% = 36 der Kehlkopfkranken waren Raucher Von 18 Larynxcarcinomträgerinnen waren 44.4% = 8 Raucherinnen welche Zahl jedoch keine statistische Aussagekraft hat in Folge der geringen Fallzahlen

TABELLE 3
LARYNXKRANKE FRAUEN 1960—1965

Altersgruppen	davon Raucher		
0—20	8	0	
20—30	34	15	44.1%
30—40	14	5	35.7%
40—50	27	9	33.3%
50—60	30	6	20.0%
60—70	18	0	
über 70	9	1	11.1%
über 20	132	36	27.2%
Larynxcarcinome	18	8	44.1%

In den Tabellen 4 und 5 sind die klinischen Bilder der Larynxaffektionen bei Rauchern und Nichtrauchern angeführt. Es stehen 140 untersuchte und behandelte Raucher 177 Nichtrauchern gegenüber Raucher erkranken wesentlich seltener

an akuter Laryngitis als Nichtraucher. Dieses Verhältnis kehrt sich beim Bild der chronischen Laryngitis um: statistisch signifikant für den 3S Test bei der chronisch katarrhalischen Form, während für die chronisch hyperplastische nur im 2S Test Signifikanz besteht. Auffällig ist das seltene Auftreten der Vorerkrankungen des Larynxcarcinoms, Leukoplakie-Pachydermiepapillomatöse Epithelverdickung beim Nichtraucher. Die erhobenen Zahlenwerte haben statistische Aussagekraft. Ähnliche wenngleich nicht so charakteristische Unterschiede ergeben sich beim Reincke'schen Ödem der Stimmbänder.

TABELLEN 4 UND 5

KLINISCHE BILDER DER LARYNXAFFEKTIONEN DER RAUCHER

			140
Laryngitis acuta		33	23.6%
Laryngitis chronica catarrhalis		53	37.8%
Laryngitis chronica hyperplastica		43	30.7%
a. Leukoplakie Pachydermie Papillom	14/10.0%		
b. Larynxpolypen	29/20.7%		
Reincke-Ödem		11	7.9%

KLINISCHE BILDER DER LARYNXAFFEKTIONEN DER NICHTRAUCHER

			177
Laryngitis acuta		109	61.6%
Laryngitis chronica catarrhalis		29	16.4%
Laryngitis chronica hyperplastica		33	18.6%
a. Leukoplakie Pachydermie Papillom	3/ 1.7%		
b. Larynxpolypen	28/15.8%		
c. Stimmbandknötchen	2/ 1.1%		
Reincke-Ödem		6	3.4%

Pathologische Untersuchungsergebnisse

Die in den Tabellen 4 und 5 gesammelten klinischen Daten haben wir insbesondere was die chronische Laryngitis anlangt, durch Probeexcisionen zu objektivieren versucht. Einerseits galt unser Interesse den sogenannten Vorerkrankungen des Larynxcarcinoms wie Leukoplakie — Pachydermie — Papillom. Raucher erkranken an diesen um vieles öfter als Nichtraucher. Andererseits haben wir alle Larynxpolypen histologisch untersucht. Die Ergebnisse sind in Tabelle 6 zusammengefasst.

TABELLE 6

LARYNXPOLYPEN HISTOLOGISCHE BEFUNDE

	Raucher	Nichtraucher
Ödematöse Polypen	6	5
Polypen mit fibrinoiden Verquellungen und amyloider Degeneration	3	
Fibrosierte Polypen	20	18
	29	23

Auffallend war dass zwischen Rauchern und Nichtrauchern kaum zahlenmässige und keine pathohistologischen Unterschiede gelegen waren. In beiden Untersuchungsgruppen waren die fibrosierten Polypen in der Mehrzahl.

In der Tabelle 7 sind die histologischen Untersuchungsergebnisse an 30 Leichenkehlköpfen gewonnen, zusammengestellt.

TABELLE 7

HISTOLOGISCHE UNTERSUCHUNGSERGEBNISSE AN LEICHENKEHLKÖPFEN VON RAUCHERN

	Raucher 30
1. Stimmband.	
Plattenepithel normal	18
Stromapapillen	9
Epithelzapfen	2
Parakeratose	4
Ödem	22
Entzündung	6
2. Ventriculus laryngis.	
Dyschylie	20
Mikrolithiasis	11
Cystische Degeneration	10
Atrophie und Fibrose	8
Entzündung	28
3. Taschenband	
Zylinderepithel	2
Plattenepithel	8
Plattenepithelkuppe	7
Plattenepithelinseln	15
Entzündung	28

Bei der Auswahl der Präparate haben wir zwei Einschränkungen bewusst vorgenommen.

1. Die Kehlköpfe entstammen Patienten der Altersgruppen 40—60 Jahre um eine möglichst gutvergleichbare Gruppe zu erhalten.

2. Die Kehlköpfe sind Leichen entnommen, die zum Zeitpunkt des Todes kehlkopfgesund waren. Dies um dem ausgewählten klinischen Material Kehlköpfe gegenüber zu stellen, die dem Tabakrauch ausgesetzt waren ohne klinisch zu erkranken.

In der Gruppe eins haben wir die Epithelverhältnisse am Stimmband zusammengestellt. Es überwog deutlich der normale Plattenepithelüberzug. Stromapapillen und Epithelzapfen sowie Parakeratose waren seltene Befunde. Hervorzuheben wäre noch ein in der Submucosa an der Grenze zwischen Stimmband und Ventrikel gelegener Ödemherd.

In der Gruppe zwei sind Veränderungen im Ventriculus laryngis vornehmlich an den Drüsen daselbst zusammengefasst. Im Vordergrund der Beobachtungen stehen die Dyschylie der Ventrikeldrüsen und die starke chronische Entzündung der Submucosa. Mikrolithiasis, cystische Degeneration oder Atrophie und Fibrose der Drüsen konnten auch häufig zur Ansicht gebracht werden.

In Gruppe drei sind die Epithelverhältnisse am Taschenband welches ja den Inhalationsnoxen am stärksten ausgesetzt ist, angeführt Vom dort ortständigen Flimmerepithel war das Taschenband nur ausnahmsweise überzogen Häufig deckte Plattenepithel entweder inselförmig oder nur am freien Rand in Form einer Kuppe Seltener war das Taschenband ganz von Plattenepithel überzogen Durch Entzündung und interstitielles Ödem ist das Taschenband oftmals auf getrieben.

Diskussion der Untersuchungsergebnisse

Mehrere Veröffentlichungen der letzten Zeit so von Meyerson, Ryan Mc Donald und Devin und vor allem von Wallner haben die klinische Bezeichnung Raucher kehlkopf immer mehr in den Blickpunkt des Interesses gerückt Unter dem Raucherkehlkehlkopf wird eine Anzahl klinischer Symptome verstanden, die beim Tabakraucher bevorzugt zu beobachten sind. Hier steht in erster Reihe die chronische Laryngitis und die Leukoplakie — Keratisation — Hyperplasie der Schleimhaut, alles Krankheitsbilder die man unter die Vorerkrankungen des Kehlkopfkarzinoms zählt. Wallner entwickelt eine direkte Reihe von der chronischen Laryngitis zum Carcinoma in situ Birnmeyer Meyerson Michailow und Rait schew und Köhn sind nicht soweit gegangen und beschränken sich darauf dass der Tabakrauch, ähnlich wie berufliche Inhalationsnoxen am Kehlkopf reversible Schäden setzt. Damit könnte allerdings eine Bahnung für die Vorerkrankungen des Larynxcarcinoms zustande kommen. Die Zahlenangaben für Raucher die am Kehlkopfkrebs erkrankt sind, schwanken innerhalb grosser Grenzen. Blümlein fand unter beruflich Kehlkopfbelasteten und Rauchern nur 17 %, Kirchner 43 %, Fior 72.5 %, Carfagni 82 % und Fusari 98 Träger eines Larynxcarcinoms. Die von uns gefundenen Zahlen von 42.4 % bei Männern und 44 4 bei Frauen welche rauchten und einen Kehlkopfkrebs bekamen, liegen an der unteren Grenze Diesen unseren Zahlen sowie den Tabellen 4 und 5 konnten wir entnehmen.

1 Raucher erkranken wesentlich häufiger an den Vorerkrankungen des Larynx carcinoms als Nichtraucher

2. Raucher erkranken unseren Untersuchungsergebnissen nach nicht häufiger am Larynxcarcinom als Nichtraucher

Ein weiteres interessantes Ergebnis unserer klinischen Untersuchungen ergab die Aufschlüsselung des Patientengutes bezüglich der Berufsgruppen 17 5 all r Kehlkopfkranken gehen einem Beruf mit Kehlkopfbelastung nach In dieser Gruppe überwogen auch die Raucher Insgesamt fanden wir unter den Kehl kopfkranken, das Kehlkopfcarcinom ausgenommen, 5/ % Raucher Diese Unter suchungsergebnisse finden eine Unterstützung und Bestätigung durch Nessel der sagt die Veränderungen des Raucherkehlkopfs sind reversibel, die allerdings durch Berufsschäden potenziert werden können, da durch diese die Abwehrmechanismen der Kehlkopfschleimhaut lahmgelegt werden können.

Es steht ausser Zweifel, dass der Tabakrauch infolge lokaler Reizwirkung die Kehlkopfschleimhaut schädigt. Die Noxe trifft wie jede andere Inhalationsnoxe am meisten das Taschenband. Dies wird auch von Buckes und Cause berück

sichtigt. Entsprechend ihrer Untersuchungen ist die Art des Epithelüberzuges der Taschenbänder abhängig vom Lebensalter und den Lebensgewohnheiten. Wir haben nun versucht den lokalen Schäden nachzuspüren und die klinischen Bilder der Larynxaffektionen der Raucher mit denen der Nichtraucher zu vergleichen. Wir sind zu folgenden Ergebnissen gekommen.

1 Zwischen den Kehlkopfaffektionen der Raucher und Nichtraucher bestehen nur quantitative und keine qualitiven Unterschiede

2. Nichtraucher erkanken häufiger an acuter Laryngitis als Raucher

3. Raucher leiden vielmehr an der chronischen katarrhalischen Laryngitis.

4 Die chronische hyperplastische Laryngitis findet sich beim Raucher häufiger als beim Nichtraucher

5 Bezeichnenderweise sind gerade die Leukoplakie, die Pachydermie und die papillomatöse Epithelverdickung eine bevorzugte wennicht sogar typische Raucherkrankheit.

6 Larynxpolypen sind beim Raucher häufiger zu sehen, jedoch bestehen im histologischen Bild zwischen den Polypen der Raucher und Nichtraucher keinerlei Unterschiede.

7 Beim Reinke schen Ödem bestehen wohl Unterschiede zwischen Rauchern und Nichtrauchern Raucher erkranken doch häufiger

8. Beim Raucher ist unserer Erfahrung die Phase der Einschränkung der glandulären Sekretion der Laryngitis stark verlängert.

Gerade diese letzte klinische Beobachtung sowie Untersuchungen von Helwig Ryan Wallner Birnmeyer Ruckes und Cause haben uns veranlasst Leichenkehlköpfe von Rauchern zu untersuchen. Wie schon eingangs erwähnt war das Material ein ausgewähltes, was die untersuchten Altersgruppen und die klinische Beschwerdefreiheit bezüglich Kehlkopferkrankungen anlangt. Um weitestgehend Berufsnoxen auszuschalten, stammten die Kehlköpfe von Personen, die keinem kehlkopfbelastenden Beruf nachgegangen waren Sehr auffällig waren die geringfügigen Veränderungen am Stimmband selbst, sieht man vom häufigen Vorkommen des von Noel beschriebenen Ödems am Übergang des Stimmbandes zum Ventriculus laryngis ab Das Vorkommen metaplastischer Plattenepithelinseln am Taschenband haben wir ebenso wie Ruckes und Cause, sowie Birnmeyer als Folge unphysiologischer Reize dem Tabakrauch zugeschrieben. Eine Schädigung der Schutzmechanismen des Kehlkopfs durch Tabakraucheinwirkung scheint uns auch aus den Befunden an den Drüsen des Ventriculus laryngis ableitbar Ruckes hat den Begriff der Dyschylie des Drusenkörpers im Recessus laryngis geprägt und versteht darunter Sekretstau, Ektasie des Drüsengangsystems mit Schleimübertritt ins Interstitium und reaktiver Entzündung Ursache für die Dyschylie sind u.a. auch Epithelmetaplasien an der Mündung der Ausführungsgänge und in den letzten Endstücken der Gänge. 65% des Untersuchungsgutes von Ruckes waren mit dyschylischen Veränderungen behaftet. In unserem Material waren sogar in 86 % der vergleichbaren Falle die Funktion des Taschenbandes, Befeuchtung des Stimmbandes, nicht unwesentlich gestort. Dabei ist allerdings in Betracht zu ziehen, dass es agonal zum Sekretstau in den Ausführungsgängen kommen kann,

Mikrolithen allerdings sind sicher Zeichen einer intravitalen Dyschylie, ebenso die Cystenbildung sowie regressive Veränderungen am Drüsenkörper wie Atrophie und Fibrose. Damit geht Hand in Hand die zunehmende Empfindlichkeit des ungeschützten Stimmbandes für berufliche und andere Inhalationsnoxen. Ob für die Dyschylie auch das resorbierte Nikotin selbst verantwortlich ist, kann kaum entschieden werden.

Aus den Ergebnissen unserer Untersuchungen haben wir zum klinischen Begriff des Raucherkehlkopfes wie folgt Stellung genommen.

1 Der Tabakrauch lässt vorwiegend über den Wirkungsmechanismus lokaler Schleimhautreizung Krankheitsbilder am Kehlkopf entstehen, die sich nur in der Intensität von Affektionen anderer Ätiologie nicht aber in ihrer Art grundsätzlich von diesen unterscheiden. Die Veränderungen erscheinen im wesentlichen rück bildungsfähig.

2. Der Raucherkehlkopf ist durch eine besondere Anfälligkeit für das Ent stehen einer chronischen Laryngitis, sowohl in ihrer katarrhalischen wie hyper plastischen Form gekennzeichnet.

3. Leukoplakie — Pachydermie — papillomatöse Hypertrophie der Schleimhaut, die Vorerkrankungen des Larynxcarcinoms entstehen bevorzugt am tabak rauch-geschädigten Kehlkopf.

4. Patholhistologische Merkmale des Raucherkehlkopfs sind
a) gehäufte Plattenepithelmetaplasien am Taschenband
b) submucöse Ödembereitschaft und entzündliche Infiltration besonders im Recessus laryngis
c) Dyschylie des ventriculären Drüsenkörpers: Mikrolithiasis, Atrophie und Fibrose.

5. Trotz der gestörten Schutzfunktion an der Schleimhaut und dem häufigen Vorkommen von sogenannten Vorerkrankungen des Larynxcarcinoms am Raucher kehlkopf, tritt dieser nur in mittelbare Beziehung zum Kehlkopfkrebs.

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BLOOD GAS DETERMINATIONS IN LARYNX OPERATIONS

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At the Otolaryngological Hospital of Helsinki Uni ersity from February 1 1965 to March 31 1966, the laboratory made blood gas analyses using th Micro-Astrup method to determine the acid-base balance of 61 patients who were operated on for larynx carcinoma. Of the patients 20 had pathological changes in their acid-base balance in the preoperative phase and 26 in the postoperative phase. The nature of the disturbances was analyzed and with the aid of the information thus obtained treatment was prescribed for the removal of the cause or for symptomatic improvement of their condition. Already in the short time since the adoption of the method it has been responsible for valuable information which has supplemented clinical xaminations; its interpretation and utilization is simpl and easily adapted to treatment in comparison t earlier methods. During examination it has been of much help, particularly in the treatment of the most seriously ill patients.

Larynx carcinoma patients are often difficult to operate on not only because of their cancer but also because of the related complications and advanced age. Improvement of the patients general condition is an important part of their treatment. The disturbances in many of the patient s vital functions, which affect his general condition, are revealed as changes in the acid-base balance. The acid base balance and changes in it can be determined on the basis of blood gas analyses done with blood samples.

THE PURPOSE OF THE INVESTIGATION

Because some 100 patients are treated annually for larynx carcinoma at the Otolaryngological Hospital of Helsinki University and in treatment the observation of their acid-base balance is useful, a Micro-Astrup apparatus, suitable for this purpose, was acquired in the beginning of 1965 By means of this apparatus it is possible to measure values related to acid-base balance at short intervals of e.g an our or 24 hours.

With the help of this apparatus it was attempted to determine the patient s acid-base balance upon admittance to the hospital or when the operation was being planned By means of preoperative samples it was attempted to improve the patient s condition so that it was favorable for the operation and to determine a suitable time for the operative procedure. The sample taken on the morning of the operation gave the starting point for estimating changes which would take place during the operation. The purpose of postoperative samples is to give information on the stress caused by the basic illness of the patient and his fluid balance the operation and possible complications.

Basic principles of acid-base balance

The criterion used for the acid-base balance of the system is the pH of the blood, the normal range being 7.35—7.42. *Acidosis* is a state where the pH is below this range. In *alkalosis* the pH is higher than 7.42. Both acidosis and alkalosis may be caused by disturbances in either respiration or metabolism, in which case the state is described as *metabolic* or *respiratory* acidosis or alkalosis. The system endeavors to restore the disturbed pH to a normal level in which case the situation is said to be compensated.

In order to determine the nature of the disturbance it is necessary to measure the pH, pCO standard bicarbonate (HCO_3) and calculate the difference between the fixed bases and acids in the system i.e. the Base Excess (BE). Their normal values can be seen as a horizontal line from th scale of corresponding values in Chart.

THE PATIENTS

Blood gas analyses were carried out on 61 larynx carcinoma patients in the period between February 1 1965 and May 31 1966 a total of 300 determinations being made. These patients underwent a laryngectomy or equally strenuous operation. The ages of the patients varied between 39 and 78

From most of the patients 2—3 samples were taken, whereas from patients in poor condition, particularly in connection with a more serious operation more than 10 samples were examined.

The blood samples were taken at the time when the operation was being planned on the morning of the operation after the operation and in the postoperative phase whenever necessary

METHOD

T make blood gas analyses by means of the Micro-Astrup method capillary blood needed for the analysis is taken anaerobically from the fingertip into four capillary tubes. An amount of 0.3—0.5 ml of blood is sufficient. The pH of the sample is examined electrically in the apparatus, after which it is equilibrated with the known CO_2 compounds and the pH values of th sample are determined. The pCO_2, HCO as well as the Base Excess value as m equiv /L which expresses th deficiency or excess of bases, are obtained from a nomogram drawn up on the basis of the Henderson-Hasselbach equation. The results are available within about 30 minutes.

RESULTS

Calculations of the patients acid-base balance made on the basis of blood gas analyses at the time the sample was taken appear in Table. The condition was considered pathological when at least one of the examined parameters was beyond normal limits. The diagnosis for 10 patients was not made in the preoperative phase and for 14 patients in the postoperative phase, so the preoperative condition can be judged in only 51 cases and the postoperative condition in 47 cases.

Preoperative findings

Among the patients examined in the preoperative phase there were 20 who had several types of disturbances in their acid-base balance. Additional changes due to compensation were observed in 5 cases out of 10 in respiratory acidosis, in 4 out of 12 in metabolic acidosis and in 5 patients out of 8 in metabolic alkalosis.

TABLE 1

BLOOD GAS DETERMINATIONS IN LARYNX-CA OPERATIONS

	Preoperative		Postoperative	
Number of patients		51		47
Normal finding		31		21
Pathological finding		20		26
Respiratory acidosis				
Uncompensated	5		16	
Compensated	5		1	
Total		10		17
Metabolic acidosis				
Uncompensated	8		3	
Compensated	4		5	
Total		12		8
Respiratory alkalosis		3		6
Metabolic Alkalosis				
Uncompensated	5		3	
Compensated	3		1	
Total		8		4
Improved by treatment		10/20		21/26

Postoperative findings

In the postoperative phase the condition of 47 patients was appraised, and over half, viz. 26 patients, were found to have a disturbance in the acid base balance. Much fewer compensation phenomena were noted than in the preoperative diagnosis. There was compensation of respiratory acidosis in only 1 case out of 17 while compensation of metabolic acidosis was evident in 5 out of 8 patients. In the group of 4 with metabolic alkalosis only 1 was compensated

Treatment and its effect on the results

Most of the patients examined had infections as well as functional deficiency of the heart and blood circulation The medication consisted of antibiotics and heart medicines. Respiratory insufficiency was treated by means of active ventilation and breathing exercises supervised by the medical gymnast. In addition aerosol therapy was used in which water vapor is supplemented by aerosol preparations which loosen mucus. In the treatment of metabolic acidosis we also used bicarbonate solutions in addition to the usual fluid and respiratory treatments.

Case history

Chart presents the effect of care on disturbances of the acid-base balance of a patient who is in poor condition. A 41 year old male patient, E. K., came to the hospital out-patient department on Saturday night, December 10 1965 in a serious state of asphyxiation due to constriction of the air passage in the larynx caused by an inflammation and a tumor as well as heart insufficiency Even after an emergency tracheotomy the patient had serious respiratory insufficiency which, however the metabolic acidosis compensated so much that the pH was nearly normal. After eight weeks of intensive respiratory treatment and medication the patient was in condition for an operation. For determination of the patient

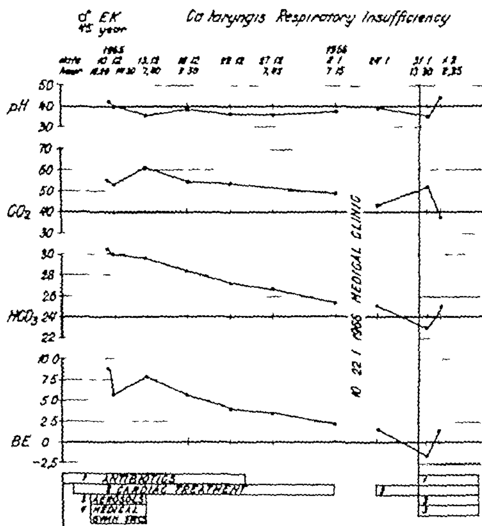


Fig. 1

liver function he was examined also at the Hospital for Internal Diseases. An operation was performed on January 31 1966 Having successfully undergone the operation the patient recovered quickly from the slight disturbances in fluid balance caused by it

Results of the treatment (Table)

Judging on the basis of blood gas analyses the condition of the patient improved in the preoperative group in 10 cases out of 20· in the postoperative phase the acid base balance improved during treatment in 21 cases, which is about 80 % of the total of 26 patients in the group.

DISCUSSION

Earlier it was difficult to examine the acid-base balance of larynx carcinoma patients because of the lack or complicated nature of the equipment necessary. Consequently it was mostly omitted. The electrical blood gas analysis method developed by Siggaard-Andersen and Astrup (Astrup 1956, Jorgensen and Astrup 1957, Siggaard Andersen 1963) was obtained for the Otolaryngological Hospital in the beginning of 1965.

The team using the Astrup apparatus quickly became familiar with the micromethod; the results which have been achieved with it have proved to correspond to results received from the same samples in other laboratories. Due to a lack of staff the acid-base balances were obtained only for 61 out of a hundred larynx carcinoma patients who received treatment and in some of these cases only in the pre- or postoperative phase. Taking an anaerobic sample from the fingertips, at least of the larynx patients, proved easier than taking it from the earlobe.

Although the Base Excess reveals, even when the pH is normal, e.g. metabolic acidosis which has no clinical symptoms (Howland and Schweizer 1963), it is not able to reveal the primary cause in a compensated disturbance; this is best discovered by clinical observations (Harri, 1962). Regardless of these minor problems, it is unnecessary to continue the so-called alkali reserves examination in addition to the Micro-Astrup procedure, because it does not give a picture of the patient's metabolic state (Nunn 1962).

In observating the results, it is noticed that in the preoperative phase half of the patients were able to compensate respiratory acidosis by means of metabolic alkalosis, which requires the kidneys to adapt to the existing disturbed condition and its correction. The same tendency to compensate, but with the aid of the respiratory system, was observable also in the groups with metabolic acidosis and alkalosis. In the samples taken in the postoperative phase the metabolism had time to correct the acidosis caused by respiratory deficiency in only 1 case out of 17. On the other hand, metabolic disturbances improved easily with the aid of respiration.

During the treatment the changes in the acid-base balance gave data for comparison on the patient's condition as well as valuable indications for treatment before a clinical change was evident. On the other hand, the worse the patient's condition the more an examination of capillary blood is misleading (Severinghaus, 1965).

One patient died of uremia, the progress of which the blood gas analysis graphically demonstrated. One patient had irreversible brain damage due to heart failure; in treatment it was possible to use blood gas analysis values quickly to advantage.

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Kaskisaari
Helsinki 34.

DISCUSSION

Peter Berdal, Oslo Norway

In Norway laryngeal carcinoma is less frequent than in the other Scandinavian countries. In particular there is a great difference between its frequency in Norway and Finland. See table 1

TABLE 1

NEW CASES LARYNGEAL CARCINOMA PER 100 000 PER YEAR

(Denmark 1957 Finland, Norway Sweden 1958)

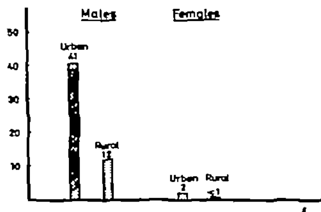
	Males	Females
Denmark	2.9	0.6
Finland	8.2	0.5
Norway	1 7	0.2
Sweden	2.3	0.3

Corresponding figures are found pertaining t the distribution of bronchial carcinoma in the Scandinavian countries, although the frequency of bronchial carcinoma in each country is about 10 times higher than the frequency of laryngeal carcinoma.

As appears from figure 1 derived from The Cancer Registry of Norway laryngeal carcinoma is in Norway mainly an urban disease. This fact points to the importance of milieu factors pertaining t the genesis of the neoplasm. Furthermore it appears from the figure that males acquire this disease far more frequently than females.

Fig. 1.

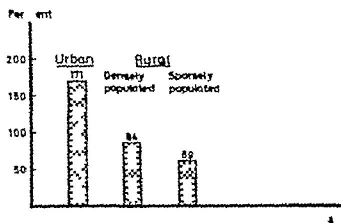
Ca. laryngis in Norway 1959 61
Incidence per 1 million per year



A comparison of the occurrence of laryngeal carcinoma in Norway and Finland demonstrates different distribution in the two countries. During the years 1958—1961 the number of new cases of this neoplasm was in Norway 41 per million per year in urban districts and 12 per million per year in rural areas. The corresponding figures in Finland were 91 per million of urban residence and 62 per million of rural residence. Thus the frequency in Finnish towns is more than twice that of the Norwegian, and in the rural areas five times as many

In Norway the frequency of laryngeal carcinoma is highest in the towns and densely populated areas as appears from fig. 2.

Fig. 2.



However there is quite a difference between different parts of the country This appears from table 2 which demonstrates from different districts the percentage of observed cases of laryngeal carcinoma related to the expected number

TABLE 2

CARCINOMA LARYNGIS IN NORW Y 1958–62. RATIO BETWEEN BSERVED AND EXPECTED NUMBER F CASES IN PER CENT ACCORD NG TO RESIDENCE. MALES

Oslo	Bergen	T lemark	Oppland	Finnmark
177	211	146	33	211

Telemark is partly a densely populated industrial county and partly it is sparsely populated with its inhabitants occupied in agriculture forestry and fishery Oppland is a parsely populated county where th livelihood is mainly agriculture and forestry Finnmark, too, is a sparsely populated area with littl industry and it is astonishing t find predominance f laryngeal carcinoma there The reason for this we don t know An accidental circumstance can at th time being not be definitely excluded. It might be mentioned that another kind of malignant tumor also — for unknown reasons — occur with predominance in the northern part of the country namely papillomatous thyroid carcinoma in young women.

Regarding separat causal factors tobacco smoking is t be blamed in a great number of cases. Siirala has today called attention to th importance of prolonged upper respiratory infections and a similar tiologic rol is possibly played by respiratory inflammations of non infectious kind. Grahne suggests that the high temperature frequently used in the Finnish sa na may be of importance Undoubtedly mor milieu factors may influence the dev lopment of these malignant growths.

Regarding the question of which are the more basi factors in the genesis of laryngeal carcinoma it has t be l ft t the future t be solved.

Address: Rikshospitalet Oslo.

B. Mårtensson, Karolinska Sjukhuset, Stockholm to Rygård.

The difference in cure rates for glottic carcinomas with subglottic extension that exists between our materials (69 % against 38 %) has partly been explained by dr Rygård by the high frequency of femal patients in his group.

But another part of the explanation is that th results of treatment in my material are presented as the 5-year cure rate after the primary treatment alone, whereas in dr Rygårds material the recurrences after irradiation which are cured by secondary surgery are counted as 5-year cured.

I would also ask dr Rygård if he has many low-grade carcinomas among the irradiated cases in the group with subglottic extension? If so this may also contribute to a high survival rate.

TABLE 1

5-YEAR CURE RATE IN LOW-DIFFERENTIATED CARCINOMAS

	Irradiation		Surgery	
Glottic T_1	9/14	64 %	0/0	
Glottic T_2	5/7	71 %	0/0	
Glottic T_3	11/16	69 %	5/15	33 %

As the table shows we have found that the low differentiated carcinomas respond very good to irradiation irrespectively of their extension. The cure rate is as good in group T_3 as in group T_1

As a consequence of this finding we now always treat a low grade carcinoma with primary irradiation.

Jørgen Rygård Copenhagen, Denmark to Mårtensson.

As an answer to your question concerning the rather high cure rat in those glottic cancers, that invade the subglottic region I can only comment that 8 of the 41 cases were women and they did better than the men: 7 out of the 8 survived for more than 5 years symptomless. So far as the histologi grading of the tumours is concerned, this has not affected the choice of primary treatment in the material from the Radium Centre.

B. Mårtensson. Closing words

It is still *early to say whether tumours with very limited subglottic extension*, that we now can diagnose by transconioscopy should be treated by irradiation or not. Our follow-up time is too short. But we know that such case shall never be treated with the narrow irradiation-fields that are common in the treatment of pure glottic carcinomas. W now treat them by cobolt using wide fields.

Another important point concerns the control of these cases after irradiation. It is not enough to check them by indirect and direct laryngoscopy The follow-ups must include an inspection of the subglottic space by angle optic in order to detect a subglottic recurrence.

Address: Karolinska Sjukhuset, Stockholm.

Rygård to Holsti

The question of whether primary irradiation or primary operation gives the best survival rat has to my mind only been elucidated by Dr. Lederman, who in 1965 reported on such two materials from The Royal National Throat, Nose and Ear Hospital. In spite of th fact that the primarily irradiated group of 152 patients contained relatively more patient in the higher stages of disease (U.I.C.C.) the cure rate of 61 % 5 years survival was not different from the cure rate of 63,8 % for the 141 patients that primarily were operated upon, and of the primarily irradiated patients only 23 % had to undergo some form of surgery whereas 50 % of the primarily operated patients had total laryngectomy and 50 % partial laryngectomy

Address: Radiumstationen, København Ø.

COVER

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SUPPLEMENTUM 225

TREATMENT OF LARYNGEAL CANCER

A Study of 638 Cases

BY

SIRKKA LAUERMA

ACTA OTO-LARYNGOLOGICA NARVAVÄGEN 15, STOCKHOLM NO

FROM THE OTOLARYNGOLOGICAL HOSPITAL, UNIVERSITY OF HELSINKI (HEAD PROFESSOR URPO SIIRALA M.D.) AND FROM THE RADIOLOGICAL HOSPITAL, UNIVERSITY OF HELSINKI (HEAD: PROFESSOR SAKARI MUSTAKALLIO M.D.)
HELSINKI, FINLAND

ACTA OTO LARYNGOLOGICA

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During the many years consumed in producing this study Miss Aino Nikupaavo, M.A., librarian of the Otolaryngological Hospital of the University of Helsinki, spared no effort searching for relevant publications among the vast literature dealing with laryngeal cancer. She also compiled the bibliography. I wish to acknowledge my debt to her.

The translation into English was done by Paul Sjöblom, M.A.; Aarno Kohonen, M.D., assisted in reading the proofs. My thanks to both of them!

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Finally my husband, Raimo Lauerma, Ph.D., deserves special mention for his interest in the progress of my work and for his careful reading of the manuscript, which resulted in the rectification of many an inaccuracy and in the improvement of its style.

Helsinki, October 1967

Sirkka Lauerma

I INTRODUCTION AND SCOPE OF THE STUDY

Cancer in the larynx is a malignant tumor that, compared to many other kinds of cancer is relatively easy to treat. In most instances, the tumor shows clear symptoms at its initial stage and effective treatment given at this stage is likely to give good or reasonably satisfactory results.

Since 1947 the *World Health Organization (WHO)* has published statistics on the incidence of cancer in different countries. Thus, information on a fairly broad scale is available on the numbers of cancer patients (morbidity) cancer mortality and the age and sex of the patients.

According to *WHO* statistics covering 35 countries, in the year 1961 for example an average of 1.2 persons out of every 100,000 inhabitants of these countries died of laryngeal cancer The corresponding figure for Finland was 1.3.

The *Finnish Cancer Register* was established in 1952 on the initiative of the Cancer Society of Finland, and since 1953 reliable data have been available on the incidence of various cancers in Finland *(Sarén* and *Hakama* 1964) According to these data, 110 new cases of laryngeal cancer were diagnosed in Finland in e.g., 1959 The frequency of occurrence of cancer of the larynx in the year mentioned was 3.2 per 100 000 population, and this disease accounted for 1 4 per cent of all cases of cancer reported in this country In the same year the frequency of carcinoma of the lung and of the bronchus amounted to 14 1 per cent of all the cases of cancer Even though the percentage of the total incidence of the disease registered for cancer of the larynx is low compared to that for carcinoma of the lungs, laryngeal cancer must nevertheless be considered a not uncommon variety of cancer

Comparisons between the results obtained in the treatment of this malady in different countries and in different hospitals have been rendered difficult up to recent years by the fact that there has existed no internationally accepted classification of for example, the exact anatomic site and extent of cancer of the larynx. Either each hospital has classified its own cases in its own way or no precise system has even been formulated. The patients have been treated mostly on the basis of the experience gained in the past by each hospital and the attending physician.

Several international commissions, for example, *WHO Union Internationale contre le Cancer (UICC)* and the *American Joint Committee on Cancer Staging and End Results Reporting* have been working since the early 1950's to establish an international classification. The purpose of the so-called T.N.M. system and the clinical staging of tumors is to help the clinician plan his treatment and to give information on the prognosis of lesions. In addition, in the frame of reference of a classification, it would be possible to describe the results of therapy with considerable precision and to compare them reliably with the corresponding results achieved by other hospitals.

If the majority of the hospitals treating cancer of the larynx in all the different parts of the world could be induced to adopt the T.N.M. system and all the likely types of classification of tumors and to bring them into general and uniformly applied use

then the indications for treatment in laryngeal cancer might be made fa
more reliable and the results of therapy obviously improved to a signifi

Even by international standards, a large number of laryngeal cancer
treated each year at the Otolaryngological Hospital and at the Radiologi
of the University of Helsinki Because in addition, different hospitals have
ideas on methods of treatment it has been deemed advisable to carry ou
the treatment of laryngeal cancer on the basis of the material collect
hospitals.

In the light of her own research, the author first deals with the distrib
material according to the age and sex of the patients, the anatomic site a
the tumors and their histology The title of the present study implies
examination of treatment but, inasmuch as many interesting features ar
with the age and sex of the patients and the anatomical and histological c
of the tumors, it was considered pertinent to include them in the discussion

On the basis of the results obtained, an attempt has been made to evaluat
to which the aforementioned factors have affected the patients prognoses

*The matters of principal concern have been the m thods of treatment an
achieved together with comparisons between them Attention is furth
recurrences of the disease and to the possibilities of saving patients in such*

II GENERAL REVIEW OF LITERATURE ON DIAGNOSTICS AND TREATMENT

In his historical review Sir *St Clair Thomson* (1939) relates th t laryngeal cancer was known as early as the first couple of centuries of the Christian era, when the disease was referred to by for example, *Aretaeus*, and described by *Galen* The Middle Ages are lacking in records, and not until the Rennaissance did the disease begin to attract medical attention. *Boerhave* in 1668 described cancerous angina, and in 1732 *Morgagni* is reported to have given a clear description of two cases of laryngeal cancer (*Op cit.*)

One of the major forward steps in the diagnostics of cancer of the larynx was taken with the invention of mirror laryngoscopy (*Babington* 1829 *Garcia*, 1854–1855, *Turck* 1858, *Czermak* 1858) which made possibl bservation of the larynx through the mouth and largely removed the difficulties that had hampered examination of the larynx of patients.

A second great step ahead was taken, when *Virchow* (1958) lucidated the histological differences by which a malignant tumor can be distinguished from other kinds f tissue.

In recent decades new methods f examination have been devised and developed for the purpose, on the one hand, of discovering the presence of the malignancy as early as possible and, on th other of ascertaining the extent of the tumor after its discovery in the larynx before treatment.

In indirect laryngoscopy major differences in th motility of the vocal cords can be bserved, but slight impairment of movement is liabl to escape notice in this kind of examination. Stroboscopy examination, however is ery well suited t the observation of slight changes in the movements of the vocal cords and for this reason it affords valuable method of making an early diagnosis of carcinoma of the vocal cords (*Schönhärl* 1962)

The laryngeal microscope contrived by *Kleinsasser* (1961 b, 1962) is particularly pplicabl to the examination of precancerous conditions and early-stage cancer in the larynx.

Retrograde examin tions of the larynx were performed as early as the mid-nineteenth century (*Neudorfer* 18.8). Through tracheostoma a mirror was inserted beneath the larynx into the trachea for observation of the subglottic region and the lower surface of the vocal cords. The same principle is applied in transconioscopy Studies involving transconioscopy have been carried out and published in recent years by among others, *Mårtensson et* l. (1964), *Kirrranta* (1966) and *Mårtensson* (1967).

The subglottic region can also be observed by using the telescope (larynxendoscope) developed by *Müller* (1954) It is also well suited to the examin tion of the ventriculus Morgagni and the laryngeal surface f th epiglottis.

X ray examinations of the larynx are an important factor in the diagnosis of laryngeal cancer (*Jackson* and *Norris* 1961) Tomography has proved to be the most effective procedure (*Gross* 1960) It makes possible the investigation of the depth of a tumor as, for example, probing into the ventriculus Morgagni and the subglottis. In recent years various methods applying contrast media (laryngography) have been developed for the investigation of the extent of laryngeal malignancies. Among studies dealing with the subject, noteworthy are those by *Ogura* et al. (1960) *Ogura* (1962) and *Lau* (1962)

A specimen of tissue must always be taken and histologically examined to confirm a diagnosis of laryngeal cancer before treatment is undertaken. In order for the specimen to be obtained from the right place the patient should be prepared well for the measure by means of, for example suitable premedication and the anesthetization should be sufficient. In the case of patients hard to handle, the measure might also be carried out by resorting to general anesthesia (*Leicher* 1963 b) In cases where the specimen does not indicate the presence of a malignant tumor but the clinical picture of the larynx nevertheless arouses suspicion of cancer the biopsies should be repeated at short intervals (*Leicher* 1963 b)

In certain cases clinical appearance points to cancer but even repeated biopsies produce no cancerous tissue. In such cases, in order to obtain the specimen from exactly the right place, it may be necessary to split the larynx along the midline (laryngofissure) and take a specimen under direct inspection (*Link* 1962)

Palpation of the neck plays an important rôle in the examination of a patient (*Jackson* and *Norris* 1961) In the light of the palpation finding, it is possible to some extent to determine whether the malignancy has spread to the lymph nodes or not. *Zange* (1955) emphasizes the importance of palpation in detecting lymph node metastases. It must nevertheless always be borne in mind that every enlarged lymph node palpable in the neck does not signify metastasis (*Leicher* 1963 b)

The oldest records of surgical measures in the treatment of laryngeal cancer are connected with the history of tracheotomy Evidently many of the earliest tracheotomies were performed precisely on account of the occurrence of a malignant tumor in the larynx. The celebrated surgeon *Antyllos* (c. A.D 140) was the first to explain in detail the performance of a tracheotomy and he himself also performed this operation (*Sercer* 1962)

Since the 18th century reports have been published on cases in which laryngotomy (splitting the larynx along the midline) has been employed to remove foreign objects and benign tumors from the larynx (*Leicher* 1963 b) The first surgeon to remove a tumor by performing a laryngotomy was *Ehrmann*, who did it in Strassburg in 1844 *Buck* performed a similar operation in the United States in 1851 (*Buck* 1853) In the early 1900's numerous articles were published on the performance of laryngofissure in the treatment of carcinoma of the vocal cords, and the results achieved with this therapy were fairly good. *Jackson* (1915) wrote in his book Peroral Endoscopy and Laryngeal Surgery "In an early intrinsic malignant growth of very limited extent not involving th posterior portion of the larynx, the results of thyrotomy (laryngofissure) have been positiv ly brilliant (*Jackson* and *Norris* 1963)

Laryngofissure was, indeed, for several decades the most frequently performed conservative operation. During the past two decades several partial resections have been developed and adopted in practice, noteworthy among them being *Alonso*'s (1950 1951) horizontal, partial laryngectomy *Leroux Robert*'s (1957 1961) frontolateral technique and *Ogura*'s (1958) supraglottic, subtotal laryngectomy together with a radical neck dissection.

In 1829 *Albers* carried out an experimental removal of the larynx of a dog. It was *Watson* who in 1866 for the first time removed a human larynx (*Foulis* 1881) His patient was a 56-year-old man with stenosis of the larynx resulting from lues. Three years following the operation the patient died of pneumonia. In 1873 *Billroth* for the first time successfully performed a total laryngectomy on a patient with cancer of the larynx (*Gussenbauer* 1874) The patient lived for seven months after the operation but died when the growth recurred.

Improvements began to be made in the techniques of total laryngectomy as early as the late 1800's (*Gluck* and *Zeller* 1881 *Gluck* 1899) and operative mortality was reduced during succeeding decades from about 50 per cent to approximately five per cent. *Soerensen* (1930) published a paper on 470 total laryngectomies, which *Gluck* and he had performed. Thirty per cent of these cases were symptomless five years after the operation and the operative mortality was five per cent. The laryngectomy technique perfected by *Gluck* and *Soerensen* (1922) is being used to this day nearly unchanged.

Crile (1906) reported a series comprising 132 cases of carcinoma in the region of the head and the neck in which he performed a radical neck dissection to remove glandular metastases. This surgical procedure was only slightly used for a long time until *Martin* et al. (1951) published a material consisting of 1 450 cases and at the same time described in detail the method of performing the operation. Also *Ogura* and *Bello* (1952) as well as *Pietrantoni* (1955) ha e confirmed through their studies the value of radical neck dissection in surgery of laryngeal cancer

Since the beginning of the present century reports ha been published on laryngeal cancer cases that have been treated by irradiation (*Delavan* 1902, *Morton* 1903, *Scheppegrell* 1905) At the first international congress of laryngologists held in Vienna in 1908, however, *Gradenigo* still expressed the view that irradiation had no real significance in the treatment of cancer of the larynx.

In 1927 *Finzi* and *Harmer* presented their material on growths in the vocal cords that they had treated by implantation of radium needles.

In the 1920' *Coutard* (1932) developed his method f protracted fractional irradiation. By means of prolongation f treatment and limitation of single doses, it was possible to old the frequently fatal accidents sustained previously by th administration of the irradiation dose required to destroy a tumor all at one sitting. The "Coutard technique is the basis for the radiological method f treating laryngeal cancer in general use today

During the past couple of decades radiotherapy has established itself as an important technique in the treatment f cancer of the larynx.

Megavoltage therapy notably cobalt therapy has stirred interest in recent years. Cobalt therapy has been recommended particularly as a preoperative measure (*Wullstein* et al. 1961 *Taskinen* and *Holsti* 1966) In operations performed after cobalt

therapy fewer complications have been observed than after ordinary X ray therapy and the operation can be undertaken in as short a time as from one to six weeks after the termination of therapy involving a full tumor dosage (*Wullstein* et al. 1961)

Chemotherapy is nowadays of only slight significance in the treatment of laryngeal cancer It has so far been applied only in advanced cases of cancer in which other treatment would be precluded. *Haas* (1962) and *Harrison* (1965) have treated cases of laryngeal cancer at an advanced stage with chemotherapeutic substances and noted a retardation in the growth of the malignancies and even, to some extent, regression.

III REVIEW OF LITERATURE IN FINLAND

The earliest report relating to laryngeal cancer n the medical literature of Finland dates back, so far as is known, to the year 1859 Visiting Vienna in that year *Sirelius* had become acquainted with the art of mirror laryngoscopy as applied by *Czermak* and passed his knowledge on to his Finnish colleagues upon his return home (*Sirelius* 1859).

In 1864 *Hjelt* reported one case of laryngeal cancer nd another in 1873.

Runeberg (1888) wrote an article on Kaiser Frederick III s cancer of the laryn and the dispute among the physicians assigned to his case

The first major study on laryngeal cancer to appear in Fi l nd was brought out by *af Schultén* in 1891 Investigating th matter of d agnosing cancer of the larynx, he reached the conclusion that the only way to make sure f the existence of a malignant disease in the larynx was to examine the tissu under a microscope

In 1914 *af Forselles* (1914 a) presented his own material, which comprised eight cases f laryngeal cancer and one case f sarcoma of the larynx. He contended that malignant growths in the larynx, particularly carcinomas that have orign ted in th vocal cords, afford comparatively f v rable opportunities for their radical removal. He also emphasized the importance of m croscopically studying the tissue.

In the same year *af Forselles* (1914 b) dealt with the aforementioned questions at a Scandinavian congress of otolaryngologists in Stockholm.

Up to the yea 1966 seven papers dealing with the histology of laryngeal cancer had been published in Fi l nd The earliest article on the subject was written by *Meurman* (1919) and it dealt w th among other things, the epithelial fibers present in epidermoid carcinoma of the l rynx. His conclusion was that all pathological cells have a tendency to form fibrous material. A subsequent study of his (1936) del ed into the histology of intrinsic cancer of the larynx. He observed: "We hav seen in these specimens various structures in the cancer growth and moreover in some, different structures sid by side n the same specimen.

Mustakallio (1946) considered in his article the question as to th extent to which the histological ppearance of a laryngeal cancer indicates the sensiti ity of the tumor to radiation. His mat rial included 67 cases treated by irradi tion, which he divided into four microscopi grades ccording to *Broders* malignogram. In the light of the therapeutic results, he rri ed t the conclusion that insofar as the t mor belongs, on the basis f its microscop ppearance, to the fourth stage or is highly naplastic radiation therapy is likely to prov more ffecti than surgery

Niskanen (19 1) discu sed the histology of keratosi f th larynx and concluded that keratosis can scarcely be regarded precancerous condition. It is neverthele con ceivable, he stated, that keratotic changes in th larynx might at a later date develop into carcinoma in onsequence f which cases f keratosis should be kept under continued observation.

Björk and *Teir* (1957) published a study dealing with benign and malignant papillomata in the larynx. The authors reached the following conclusions In the presence of a papillomatous laryngeal tumour in adults, malignancy should be suspected independently of the clinical picture which fairly often appears quite innocent even in malignant papillomas. Intraepithelial anaplastic changes are of utmost significance in determining malignancy infiltrating cancer seems to occur only in a minority of cases at the stage of the disease when these patients first come under treatment. Critical distinction is necessary in evaluating the intraepithelial changes since the benign papillomas can also show some degree of atypia. Definite intraepithelial anaplastic changes should, however, be regarded as signs of true malignancy"

On the basis of the material presented in the foregoing, *Björk* and *Hakosalo* (1957) investigated the amount of mitoses in benign and malignant papillomata as well as the occurrence of pathological mitoses The authors came to the conclusion that in benign papillomata there is little mitosis, pathological mitosis being exceedingly rare. In malignant papillomata, however, mitosis is common and pathological mitosis fairly frequent.

Multanen (1958) dealt with the histo-cytologic malignancy and clinical appearance of carcinoma of the vocal cords. He observed that the histologic appearance of such tumours varies in different parts of the growth.

In 1936 *Meurman* (1936 b) published a paper describing his experiences in treating early intrinsic cancers of the larynx by surgical means. He considered the results achieved through thyrotomy and removal of the malignancy good but he also took seriously the possibility that in the future early-stage carcinomas of the vocal cords may be treated by irradiation alone. In an article published in 1952, *Meurman* stated that in cases of cancer of the larynx and the pharynx early diagnosis was the best therapeutical weapon. At the international otorhinolaryngological congress held in Amsterdam in 1953 *Meurman* (1955) described his own expanded method of thyrotomy and the results achieved by this therapeutic procedure.

Mustakallio (1944) described the technique of radiotherapy for laryngeal cancer used in Finland since 1936 and included a review of the results achieved. The five-year-cure rate in treating 38 cases of laryngeal cancer with irradiation was 24 per cent (9/38)

Lahen (1956) published a series of 100 cases treated by total laryngectomy in the years 1915—1949 in which the rate of five year cures was 46 per cent.

Virtama and *Härmä* (1959) dealt in a paper with the question as to how far delay in the commencement of therapy was to blame for the high mortality of laryngeal cancer The authors came to the conclusion that "intensification of the cancer education among patients as well as among general practitioners is advised to increase the life expectation of the patients suffering from the laryngeal cancer" (sic)

The year 1962 saw the publication of two Finnish studies concerned with the treatment of the larynx by irradiation. *Voutilainen* and *Tuovinen* published a material comprising 261 cases in which the end results — taking the usual symptomless five-year period — yielded a 59 per cent *cure* rate. *Lauerma* and *Surala* presented a material comprising 169 early-stage cancer cases The patients had received primary radiation therapy and the total five year-cure rate was 85 per cent. The first-stage

carcinomas of the vocal cords formed the group yielding the best results of the 52 cases treated, 50 were symptomless after five years (96 per cent)

Kyttä (1964) dealt in his academic thesis with the problems of esophageal speech in laryngectomized patients.

Koulumies et al. (1964) studied the effect of the radiation treatment given in cases of laryngeal cancer on the function of the thyroid gland. The authors noted that the thyroid gland appears to be relatively resistant to ionizing radiation and that insofar as changes of function do occur they are not lasting.

Kiviranta (1966) described the technique of transconioscopy and asserted that it complements peroral endoscopy and roentgentomography of the larynx in a rapid and simple way

In 1966 *Taskinen* and *Holsti* published a study dealing with the results of radiation treatment of laryngeal cancer The material comprised 189 cases that had received primary X ray therapy 66 per cent of them having been supraglottic tumors. The five-year-cure rate for the entire series was 50 per cent (94/189) In first-stage growths, the cure rate was 80 per cent (32/40)

At the Scandinavian otolaryngological congress held in Helsinki in 1966, three Finnish papers dealing with cancer of the larynx were read. In the study published by *Surala* and *Sürala* (1967) on the epidemiology of laryngeal cancer particular attention is given to the possible effect of tobacco smoking on the genesis of this disease. The authors express the view that smoking tobacco and bad teeth do have a significance in causing cancer of the larynx.

Surala and *Lauerma* (1967) discussed the metastasization of laryngeal cancer to the lymph nodes of the neck as well as the factors affecting metastasization.

Ruska and *Lauerma* (1967) compared the functioning of the larynx of 14 thyrotomy patients and 24 patients given primary radiation therapy On the basis of phoniatric follow-up examinations, the investigators observed that the larynx of the patients treated by irradiation functioned significantly better than that of the thyrotomy patients.

IV MATERIAL AND METHODS

A General

The material comprises 638 cases of laryngeal cancer treated at the Otolaryngological Hospital and Radiological Hospital of the University of Helsinki during the years 1949—1959

In the following (Table 1) the cases are divided according to the year of inception of treatment. Furthermore, the total number of cases of laryngeal cancer diagnosed in Finland in the years 1953—1959 is reported (*Finnish Cancer Register* 1953—1956 1957 1958 *Saxén* and *Hakama* 1964) No reliable information for the years 1949—1952 is available.

TABLE 1
Annual number of cases of laryngeal cancer in the present material and in Finland

	Number of cases in material	Total number f cases in Finland
1949	44	?
1950	35	?
1951	60	?
1952	57	?
1953	53	110
1954	61	118
1955	47	90
1956	63	118
1957	68	120
1958	70	124
1959	89	140
Total	638	—

The data concerning the patients have been compiled from the case histories of both the aforementioned hospitals. A separate punched card was made out for each case including the information needed for this study in a suitable code The material has been handled almost exclusively by consulting these cards.

The case histories have been painstakingly drawn up owing, no doubt, to the fact that both the hosp tals in question are educational institutions affiliated with the University Th anamnestic data have been compiled and the examination of the patients performed according to fairly uniform principles. Thus the cases are quite comparable in th respects mentioned The surgical reports, on the other hand, are not

altogether uniform for the reason, perhaps, that during the eleven-year period covered by the present study the operations were performed by a dozen or more different surgeons.

B Follow up investigations

The follow-up examinations of all the patients who received radiation therapy wer carried out up to the year 1958 by the Radiological Hospital of the University of Helsinki. The patients reported for follow up examinations at three-month intervals after treatment was discontinued and starting with the second year at half-year intervals up to the end of the fifth year If cause was found, the patient was sent to the Otolaryngological Hospital for examination. There the larynx was examined and any required specimens of tissue taken. After 1958 the patients first visited the Otolaryngological Hospital for a follow-up examination and then, taking along the laryngologist s report, the Radiological Hospital.

Five years after the termination of therapy the symptomless patients were removed from the group kept under follow up observation. The Radiological Hospital never theless made inquiries into the health of these ex patients by letter either directly from the individuals themsel es or from their personal physicians. Continued inquiries also enabled the hospital to ascertain the date and cause of death of deceased ex patients.

During th early years f the material, the follow up examination of patients treated solely by surgery was not organized on as regular a basis as that of the radiotherapy patients, but later on ever greater attention has been paid also to the follow up observation of surgical patients.

All the operations included in the material were performed at the Otolaryngological Hospital of the University f Helsinki. In a few instances, the patient received post operative radiation in a different community after which he isited the Otolaryngological Hospital for follow-up examinations.

C. Histology

In all the cases included in the material, the nature f the tumor in the larynx had been erified by biopsy before treatment was begun, the specimen of tissue being analyzed as either cancer (carcinoma epidermoides) or its preliminary stage (carcinoma in situ)

During the years 1949—1959 several different methods of histologically classifying laryngeal cancer were used at the Otolaryngol gical Hospital of the University of Helsinki For the sake of achieving a uniform classification for the present study all the histological specimens vailable in the archives of the Hospital were gone through once more In only 55 cases the original histological specimens could no longer be found. These cases were classified on the basis of the reports that could be obtained on them.

D Determinant and indeterminant cases

According to international practice, the therapy given a cancer patient is considered successful when he has been free of symptoms of the disease for five years after the course of treatment has ended. *The effectiveness of different methods of treatment* is usually evaluated by calculating the percentage of cures. The trouble with this approach is, however, the fact that in nearly every series there are also patients who have either died without a recurrence of cancer symptoms before the end of the five-year observation period or with regard to whose subsequent fate no information is available. In some series such cases have been pessimistically counted as failures, even when in reality the patient might be alive and well in for example, some foreign country or might have died accidentally In some other series, these so-called indeterminant cases are first deducted from the total number and the percentage of cures is then calculated from the remaining number of so-called determinant cases. These questions have been dealt with by among others, *Svane-Knudsen* (1960) and *Leicher* (1963 b)

In the present study the latter method has been used and, accordingly the indeterminant cases have been left out in calculating the results of therapy In all the tables dealing with the results, both the total number of cases and the number of determinant cases have been separately given. The indeterminant cases included in the material are presented in Table 2.

TABLE 2.
Definition of 63 indeterminant cases in the material

Cause of death	Number of cases
Coronary occlusion	7
Heart failure	9
Cerebral hemorrhage	2
Aortic aneurysm	1
Rupture of the abdominal aorta	1
Gangrene of the legs	5
Pneumonia	1
Tuberculosis of the lungs	1
Purulent pleurisy	1
Hepatocirrhosis	1
Intestinal occlusion	1
Fracture of the femur	1
Senility	2
Alcohol abuse	1
Suicidium	1
Unknown cause of death	22
Lost to follow-up	6
Total	63

The number of indeterminant cases is thus 63, or 10 per cent of the 638 cases treated. The cause of death is known in 35 cases and unknown in 22, while the fat of six patients remains unknown. The average symptomless time among the indeterminant cases between the termination of therapy and the last follow up is one year nine months. Fifteen cases could be followed up for from two to twelve months, twenty three cases from one to three years and twenty five cases from three to fiv years. The average age of the indeterminant cases is 58.1 years, or slightly higher than the average age of 55 7 years for the total material Two of the indeterminant cases are women.

E Statistical treatment

In making comparisons among the results arrived at in the study an attempt has also been made to determine by mathematical means whether the differences observed are statistically significant or not. The comparison of frequencies of occurrence has been carried out by a χ^2 test. The null hypothesis has been rejected and the observed difference deemed to be significant, when verbally stated, if the probability P of receiving the tested difference occasionally is t most 0 01 but greater than 0.001 The ther degrees of significance applied are

Almost significant $0.01 > P \geq 0.05$
Highly significant $0.001 \geq P$

Insofar as the differences between figures are not statistically significant, no P values have been included in the text.

The test used has been described in, e.g., the book Statistische Methoden by *Linder* (1964)

If because of the smallness of the figures, percentages are not given, the procedure followed has been one of marking down, for example 5/9 which signifies fi e cases out of nine.

V AGE AND SEX

The majority of laryngeal cancer patients are between the ages of 50 and 70. Rarely is a patient under 40 years of age, and in childhood the occurrence of this disease is extremely rare, indeed (*Blumlein* 1956 *Leicher* 1963 b) *Calvet* and *Lacomme* (1958) have found in the literature 27 histologically confirmed cases of cancer of the larynx in children between the ages of five and sixteen.

Here (Table 5) are figures drawn from the literature on the frequency of occurrence of laryngeal cancer in patients of different ages.

TABLE 5.
Frequency of occurrence of laryngeal cancer in patients of different ages

Author	Year	Number of cases	Under 50 years Per cent	Over 50 years Per cent
McCall and *Fisher*	1952	193	20	80
Pracolo	1952	200	51	49
Baltwell and *Putney*	1954	149	20	80
Blumlein	1956	442	19.2	80.8
Pietrantoni and *Fior*	1958	570	37.5	62.5
Glaninger	1959	325	16.8	83...
Kleinsasser	1961 a	555	21.8	78.2

The occurrence of cancer of the larynx in persons over 80 years of age is considered to be rather rare (*Novotny* 1961)

According to *Kleinsasser* (1961 a) there is no significant correlation between the site of the tumor and the age of the patient. On the other hand, he pointed out that in older patients carcinoma is more often anaplastic. Previously *Broders* (1940) had reported that carcinoma is more often anaplastic in young patients.

Pietrantoni and *Fior* (1958) mentioned in their article an observation personally communicated by *Bocca* and *Ciardo* (1958) according to which older patients are afflicted more often with carcinoma of the vocal cords and younger patients more often with supraglottic carcinoma "This fact might be due to a cancerogenic action exerted on the vocal cords by different environmental factors (alcohol, tobacco, etc.). Conversely supraglottic cancer affected relatively younger age groups, possibly owing to the cocancerogenic activity of some still unknown factors, perhaps of endogenous nature It must be stated that these are suggestions which could be confirmed only by clinical and experimental research on statistically significant data.

Certain research results concerning the percentage of women included in the material on laryngeal cancer are presented in Table 4

TABLE 4

Percentage f women of laryngeal cancer cases in previous materials.

Author	Yea	T tal number of cases	Percentage of women
Martin	1947	725	3
Baltzell and *Putney*	1954	1498	7.2
Blümlein	1956	442	4
Pietrantoni and *Fior*	1958	570	5.3
Leroux-Robert	1959	644	3
Svane-Knudsen	1960	153	7.2

Pietrantoni and *Fior* (1958) reported that in thei material they could observe no difference between the sexes with respect to the clinical behavio of cancer of the larynx.

Bockmuhl (1966) has investigated the question as to whether women become affected with cancer of the larynx at younger age than men. He studied the material comprising 16,738 patients collected by the *WHO* The ratio between the numbers of men and women in the material was 92.2 7.8 His investigation indicated th t, on the average, women contract laryngeal cancer t a younger age than do men.

The cases included in the material are classified according to sex and the age at which treatment started in Table 5

TABLE 5.

Age and sex distribution of 638 cases of laryngeal cancer

Age in years	Total number f cases	Percentage f total number f cases	Number f women	Number f men
0–30	4	0.6	3	1
31–40	48	7.6	7	41
41–50	148	23.0	5	143
51–60	223	35.1	3	220
61–70	164	25.7	4	160
71–80	50	7.8	1	49
81–90	1	0.2	—	1
Total	638	100.0	23	615

The youngest patient in the entire series is a six-year-old girl and the oldest an 85-year-old man. The average age of the patients is 55.7 years. The youngest patient in the women's group is the aforementioned six-year-old girl and the oldest a woman of 79. The material includes two other women under the age of 50, one being 25 and the other 26 years old. The average age of the women is 44.4 years. The youngest male patient in the series is 27 and the oldest 85 years old. The average age of the males is 56.1 years. With respect to the averages, it should be pointed out that the ages of the patients have been calculated in terms of full years. If they had been reckoned exactly to the day, the average age of the total series would probably advance approximately half a year.

Of the patients comprising the material, 31 per cent are under 51 and 69 per cent over 51 years of age (Table 5). Of the cases in the *supraglottic* category 37 per cent (158/430) are under 51, and of those in the *glottic* group 20 per cent (42/207). In the supraglottic group there are more patients under 51 years of age than in the glottic group ($P < 0.01$). The single patient with *subglottic* tumor is a 58-year-old man.

The youngest patient in the series is a girl born in 1950, who was found in 1956 to have a tumor in her right vocal cord. Under histological examination, the tumor was observed to be of the carcinoma in situ variety. The case was kept under observation. In an examination conducted a year later, the clinical and histological diagnosis was still the same. The patient was then given radiation therapy, which caused the tumor to disappear. After this treatment the patient has remained symptomless for more than ten years. The larynx functions well and the voice is fairly clear.

The oldest patient in the material was an 85-year-old man, on the left side of whose anterior commissure a malignant tumor was found and the left side of whose larynx was immobile. Under histological examination, the tumor was observed to be of undifferentiated type. On account of his advanced age, the patient was not subjected to surgery but was given radiotherapy. Half a year after the radiation treatment had been discontinued, a recurrence was observed in the larynx, which because of the patient's weak physical condition could no longer be treated, with the result that he died of the cancer two months later.

DISCUSSION

The maximum incidence occurred in the 51–70 years age group. The lowest incidence is to be seen in the youngest and the very oldest age groups. It may be concluded on the evidence of this material that carcinoma of the larynx is a disease of later middle age. This conclusion is in agreement with the results of earlier studies (*Blümlein* 1956, *Kleinsasser* 1961 a).

Proportionately *supraglottic* tumors occur in the present material more frequently among the younger than among the older age groups. Correspondingly *glottic* tumors occur with greater frequency among the older age groups. This result agrees with the view expressed by *Pietrantoni* and *Fior* (1958) that supraglottic tumors occur more often in younger patients and tumors in the vocal cords more often in older patients,

and it runs counter to the view presented by *Kleinsasser* (1961 a) that no correlation exists between the site of origin of cancer of the larynx and the age of the patients.

The percentage of women in the material corresponds to the figures cited in the literature (*Baltzell* and *Putney* 1954, *Leroux Robert* 1939). Women were observed to become affected with cancer of th larynx at a younger age than men do, which observation is in agreement with *Bockmühl*'s (1966) report.

VI CLASSIFICATION

A Classification according to anatomic site extent and clinical stage

Isambert (1876) and *Krishaber* (1879) for the first time classified cancer of the larynx according to its anatomic site into two types and thereby laid the foundation for the classical division of the disease into intrinsic and extrinsic laryngeal tumors. In the first group they included the tumors situated in the vocal cords, ventricles, ventricular bands and subglottic region, and in the second, tumors situated in the epiglottis, arytenoid and the marginal areas of the upper border of the larynx.

More than half a century elapsed before another step forward was taken in the classification. *Leborgne* (1955) and many other investigators proposed the division of the larynx into three anatomic regions supraglottic, glottic and subglottic. This division has been used in the 1950's and 1960's as the basis of many studies dealing with laryngeal cancer

At a meeting held in Copenhagen in 1953 in connection with an international radiological congress, a classification of malignant tumors developed by the *World Health Organization* on the basis of the anatomic site of tumors was expounded (*UICC* 1962) The classification defined exactly the anatomic regions where tumors belonged in the class of laryngeal cancer The *Union Internationale contre le Cancer* (*UICC*) was given the task of further developing the general classification of malignant diseases. The fruit of this work was the T.N.M. classification (Tumor Node-Metastasis) which the *UICC* recommended in 1962 to be adopted. The classification takes into account the site of the primary tumor its extent, the possible spread of the malignancy into the lymph nodes of the neck and the possible existence of distant metastases.

By means of the *UICC's* T.N.M. classification the clinical state of the tumor of a cancer patient reporting for treatment can be quite briefly and at the same time precisel formulated. What might be considered a drawback is the fact that the number of groups is altogether too large to permit a clear comprehensive survey while in th separate groups there are generally too few cases for a reliable statistical study

F r this reason the *American Joint Committee on Cancer Staging and End Results Reporting* (19C) combined the groupings of the T.N.M system to achieve a division into the usual four so-called clinical stages of disease. At the same time, the com m ttee somewhat simplified and made more exact the T.N.M classification.

The T.N.M classification adopted by this committee is presented in Tables 6 and 7 and the clinical tage division in Table 8. The cases included in the present material have been classified and grouped according to the method applied in these tables.

TABLE 6.
The larynx divided into anatomical regions and sites according to the T NM-system

Regions	Sites
Supraglottic	Posterior surface f the epiglottis (including the tip), aryepiglottic f ld, arytenoid, entricular bands, entricular cavities.
Glottic	Vocal cords and anterior commissure
Subglottic	—

TABLE 7
TNM classification of laryngeal cancer according to th anatomi site of origin as divided into 3 regions

Supraglottic	Glottic	Subglottic
T Tumor confined to one anatomic st within the larynx		
Tumor confined to laryn geal surface of epiglottis or to an aryepiglottic fold or to ventricular cavity or ventricular band.	Tumo confined to one ocal cord and mobility f cord remains normal.	Tumor limited to one side of the subglottic region, exclusive f the under surface f cord.
T Tumor confined to one anatomic region within th larynx		
Tumor involving the epiglottis, extending to the ventricular cavities or bands.	Tumor involving both cords with normal mobility f cords, or tumor f one or both cords with fix ation f cord	Tumor extending to two sides of subglottic region, exclusive of cords.
T Tumor extending beyond the anatomic region but confined to th larynx		
Tumor f the epiglottis and or ventricles or entricula bands extending into the cords.	Tumor extending from cords either to subglotti region to supraglottic region, i to ventricular bands or entricles.	Tumor in olving the subglottic region and xtending on/to the cords.
T Tumor extending beyond the larynx		
Tumor as in T T or T_3, but with direct extension to piriform sinus, postericoid region, vallecula or base of tongue.	Tumor as in T T or T_3, but with direct extension through cartilage to skin, to th piriform sinus, or to the postericoid region.	Tumor as in T_1, T or T_3, but with direct extension through cartilage to the skin, trachea or postericoid region.

N_0 No clinically palpable cervical lymph node( ) (metastasis not suspected)
N Clinically palpable cervical lymph node( ) that are not fixed (metastasis suspected)
N_2 Clinically palpable lymph node( ) that are fixed (metastases suspected)
M_0 No distant metastasis
M Clinical and/or radiographic evidence f metastasis except to cervical regions

TABLE 8.
Clinical staging in T N M system

Stage I	$T N_0M_0$
Stage II	$T N_0M_0$
	$T_2N_0M_0$
	$T_3N_0M_0$
Stage III	$T N_1M_0$
	$T_2N M_0$
	$T_3N_1M_0$
Stage IV	$T_4N M_0$
	$T N_2M_0$
	$T_2N_2M_0$
	$T_3N_2M_0$
	$T_4N_2M_0$
	plus any combination of T and N with M_1

In recent years, studies based on the T.N.M. system have been used in a few publications. Among them, mention might be made of studies written by *Smith* et al. (1961) *Blady* (1963) *Bryce* et al. (1963) *Taskinen* and *Holsti* (1966) and *Hesse* and *Baylis* (1966).

In the following (Table 9) the results of certain investigations are presented with respect to the relative frequency of occurrence of cancer in different areas of the larynx.

TABLE 9.
Classification of laryngeal cancer cases by various authors

Author		Total number of cases	Supraglottic Cases	Supraglottic Per cent	Glottic Cases	Glottic Per cent	Subglottic Cases	Subglottic Per cent
Garland	1952	99	26	26	67	67	6	7
Pietrantoni and *Fior*	1953	486	273	56	188	39	25	5
Gloninger	1959	325	175	54	147	45	3	1
Smith et al	1961	600	253	42	335	56	12	2
Lederman	1961	808	1 4	21	559	70	73	9
Taskinen and *Holst*	1966	189	124	66	65	34	–	–
Mårtensson et al	1967	578	64	11.1	504	87.2	10	1.7

The foregoing series comprise a total of 3 085 cases, of which 1 089, or 35.5 per cent, belong in the supraglottic class, 1 867, or 60.5 per cent, in the glottic class, and 129 or 4.2 per cent. in the class of subglottic carcinomas.

Prior to treatment, the frequency of palpable metastases of the lymph nodes (metastases suspected) is considered to depend mostly on the location of the primary growth (*Pietrantoni* et al. 1962, *Leicher* 1963 a). Following (Table 10) are the results of studies dealing with the frequency of occurrence of palpable lymph node metastases in association with primary tumors situated in different anatomic regions.

TABLE 10.

Percentages of suspected metastases according to anatomic site of laryngeal cancer in previous reports

Author	Year	Total number of cases	Supraglottic Per cent	Glottic Per cent	Subglottic Per cent
Smith et al.	1961	600	22	2.5	0.6
Ogura	1962	96	35–52	10	–
Pietrantoni et al.	1962	644	39	10	9
Taskinen and Helsti	1966	189	26	8	–
Mårtensson et al.	1967	578	18.8	4.1	10.0

The 638 cases included in the present material have been classified in Tables 11 and 12 according to the T.N.M. system and clinical stage.

TABLE 11

638 cases of laryngeal cancer classified according to the T.N.M. system and clinical stage

Stage	T.N.M.	Total number of cases	Number of supraglottic cases	Number of glottic cases	Number of subglottic cases
I	$T_1N_0M_0$	155	45	89	1
II	$T_2N_0M_0$	160	123	37	–
	$T_3N_0M_0$	124	64	60	–
	$T\ N_0M_0$	24	23	1	–
Total, Stage II		*(308)*	*(210)*	*(98)*	–
III	$T_1N_1M_0$	15	12	3	–
	$T_2N\ M_0$	45	42	3	–
	$T_3N_1M_0$	62	49	13	–
Total, Stage III		*(122)*	*(103)*	*(19)*	–
IV	$T\ N\ M_0$	11	10	1	–
	$T\ N_2M_0$	3	3	–	–
	$T\ N_2M_0$	21	21	–	–
	$T_3N_2M_0$	21	21	–	–
	$T_4N\ M_0$	13	13	–	–
	$T_2N\ M$	2	2	–	–
	T_3N_0M	2	2	–	–
Total, Stage II		*(73)*	*(72)*	*(1)*	–
Total		638	430	207	1

TABLE 12.
638 cases of laryngeal cancer classified according to anatomic site of tumor and clinical stage

Stage	Total number of cases	Per cent of all cases	Supraglottic Cases	Supraglottic Per cent	Glottic Cases	Glottic Per cent	Subglottic Cases
I	135	21	45	10	89	43	1
II	308	48	210	49	98	47	–
III	122	19	103	24	19	9	–
IV	73	12	72	17	1	1	–
Total	638	100	430	100	207	100	1

Of the cases comprising the material, 67 per cent fall into the *supraglottic* group (430/638) and 33 per cent into the *glottic* group (207/638). The number of supraglottic tumors is larger ($P < 0.001$) than that of glottic tumors. In addition, the material includes one *subglottic* tumor

The single patient with a subglottic tumor was a 68-year-old man. The primary lesion (T_1) was located immediately below the level of the vocal cords. There were no palpable lymph nodes in the neck (N_0) and no distant metastases could be detected (M_0) Under histological examination, the tumor was observed to be poorly differentiated. The patient was given primary X ray therapy and remained symptomless for more than five years after termination of treatment.

Stage I cases account for 21 per cent of the total (135/638) (Table 12) Two-thirds of them (89/135) belong in the class of tumors of the glottic region and one-third (45/135) in that of the supraglottic region. Among Stage I lesions, tumors of the vocal cords outnumber supraglottic tumors ($P < 0.001$) The Stage I cases further include the single subglottic tumor in the entire series (described in the foregoing)

Nearly one-half of the total number of cases in the series belong among *Stage II* growths (308/638, or 48 per cent) (Table 12) In the supraglottic group Stage II tumors accounted for 49 per cent (210/430) of the total, while in the glottic group the proportion was approximately the same, namely 47 per cent (98/207)

Stage III tumors make up 19 per cent of the material (122/638) and *Stage IV* tumors 12 per cent (73/638) (Table 12) Of the cases in these groups, 90 per cent (175/193) in ol e supraglottic lesions. Only 10 per cent (20/193) involve glottic lesions. This means that out of the entire supraglottic group, 41 per cent (175/430) of th patients had palpable lymph nodes in the neck upon admission to hospital. In the glotti group the corresponding figure is 10 per cent (20/207) The frequency of occurrence of suspected cervical metastases is greater in the supraglottic group ($P < 0.001$) than in the glottic group

Among the 20 cases of glottic tumor in which cervical metastases were suspected at the time treatment was started (Stages III and IV) only six tumors were still entirely limited to the region f the vocal cords ($T_1N_1M_0$ and $T_2N_1M_0$) (Table 11) In the remaining 14 ases, the lesion had already spread beyond the region of the vocal cords

($T_4N_1M_0$ and $T_4N_1M_0$) Accordingly only in three per cent (6/207) of the cases of tumors still limited wholly to the region of the ocal cords had there been palpable lymph nodes (metastases suspected) in the neck upon the patient s admission to hospital.

Among the 72 supraglottic tumors belonging to Stage IV there are four cases in which metastases were found in the lungs roentgenologically at the time treatment commenced. In the total material, the frequency of occurrence of distant metastases upon admission was 0.6 per cent (4/638)

DISCUSSION

The material presented in this in estigation deviates from those in previously published reports mainly in that the largest group consists of supraglottic tumors (67 per cent) If the Finnish cases are omitted from the series presented in Tabl 9 the proportion of supraglottic tumors aries from 11 1 per cent to 58 per cent, the verage figure being 33 per cent (965/2,894) For example, *S ane-Knudsen* (1960) considers it a generally accepted view that cancer of the larynx originates in the majority of cases in the vocal cords.

As early as 1944 *Mustakallio* drew attention to the exceptionally high proportion of supraglottic tumors in series consisting f Finnish patients. He noted that growths f the epiglottis and the upper border of the larynx occur in Finland more frequently than in other countries. The same conclusion is reached by *Taskinen* and *Holsti* (1966) in their study which comprises cases in Finland (supraglottic cases 66 per cent)

Link (1962) has expressed the opinion th t, though the number of cases of laryngeal cancer is continuously increasing the frequency of occurrence f carcinoma of the vocal cords is decreasing both relatively and bsolutely

Of the supraglottic tumors in the material t hand, only ne out of every ten (45/430) was diagnosed at an early stage (Stage I) Of the tumors in the ocal cords, on the other hand, 43 per cent (89/207) were diagnosed at Stage I. The reason for this difference is mainly that at its early stage supraglottic lesion seldom presents clear symptoms. The symptoms are often so ague, in fact, that the possibility of a carcinoma is not even taken into account. Attention t this circumstance has been drawn by among others, *Pietrantoni* and *Fior* (1958) and *Fendel* et al. (1965)

Stage IV cases account f 12 per cent f the material (73/638). Th relative number of cases of advanced laryngeal cancer to report for treatment has substantially decreased in Finland during the past 20 years. In the series reported by *Mustakallio* (1944) from the years 1936–1943, they represented 61 per cent f the total (123/201) while in the material in estigated by *Loutilainen* and *Tuominen* (1962) from the years 1950–1954 the corresponding percentage was 34 (91/261) It should be remarked, however that both the series just mentioned include only cases treated by irradiation. Moreover the manner f classifying the material applied in these reports differs from the classification used in the present study

On the basis of the present material, it may be stated that the frequency of occurrence of suspected metastases in the lymph nodes of the neck depends

largely on the location of the tumor. In the group consisting of supraglottic tumors, metastases are fairly common (41 per cent) whereas in the group of tumors in the vocal cords their occurrence is far less common. The figures correspond to those presented in the literature (*Smith* et al. 1961, *Ogura* 1962, *Pietrantoni* et al. 1962, *Taskinen* and *Holsti* 1966).

B. Classification according to histology

Just as considerable attention has been paid to the classification of laryngeal cancer according to the anatomic site of the tumor, so has it also been paid to the classification of cancer on the basis of its histological appearance in recent decades.

In the 1920's two different systems of histological classification were developed for the purpose of correlating the histological differentiation of tumors with their clinical course.

The basis of *Broders* (1920, 1926) classification is the percentage of anaplastic cells calculated from a histological specimen. He divided carcinomas into four grades according to their malignancy. Grade I contains less than 25 per cent of anaplastic cells, Grade II from 25 to 50 per cent, Grade III from 50 to 75 per cent, and Grade IV – or the most malignant stage – from 75 to 100 per cent. *Broders'* histological classification was in very wide use for more than two decades, being applied to carcinomas of all organs as well as to sarcomas and brain tumors.

Compared to *Broders'* classification, the histological classification of tumors into three differentiation stages expounded by *Duval* and *Lacassagne* (1922) was far less commonly applied, especially during the 1920's and 1930's. Here is their system:

1. Epidermoid carcinomas in the strict sense
   a) cutaneous type with real keratin pearls
   b) mucous type (parakeratosis)
2. Undifferentiated or basocellular carcinomas
3. Intermediate type

Kleinsasser (1961 a) used this classification as the basis for his own system, dividing carcinomas into three groups as follows:

1. The well differentiated prickle-cell cancer
2. The poorly differentiated prickle-cell cancer
3. Undifferentiated carcinomas

Similar classifications, in which tumors are divided according to the stage of their histological differentiation into three groups, have been expounded by, among others, *StClair Thomson* and *Colledge* (1930), *Blümlein* (1951) and *Ormerod* and *Shaw* (1956). The chief features in all the aforementioned histological differentiation systems of classification are the same. *Blümlein* (1951) emphasized that the microscopic picture presented by a carcinoma is invariably more or less variegated and that the histological classification of cancer must be based only on the general impression to be obtained from the cancerous tissue. *Kleinsasser's* (1961 a) classification is based on the general picture of the tumour rather than on the details of individual nuclear

anomalies" He further laid stress on the fact that histological classification must be carried out on the basis of the differentiation stage prevailing in each lesion. This procedure he maintains, prevents classifying cases wrongly most of the time

In the 1930 s, in addition to the three aforementioned differentiation stages, yet a fourth category received recognition, namely carcinoma in situ. *Altmann* et al. (1952) published a report on 312 cases of cancer of the laryn among which they discovered 29 cases of carcinoma in situ. In their paper they presented the histological and clinical picture of these cases. Regarding the histology of the carcinoma in situ form, they wrote "Intraepithelial carcinoma of the larynx shows essentially the same cellular characteristics as ordinary squamous cell epithelioma. The main distinguishing feature is its peculiar spread within the epithelium instead of infiltrating growth into the underlying stroma. It is felt that the diagnosis of cancer can be based on the cellular changes within the epithelium alone and must not depend on the presence or absence of a more or less accidental feature uch as infiltrating growth. Cancer in situ is, therefore, regarded as true cancer from the beginning and not as a precancerous condition.

With regard to the relative frequency f occurrence of tumors at the carcinoma in situ stage, reports vary (*Kleinsasser* and *Heck* 1959) The ratios vary between the values of 0.4 100 and 18 100 (*Altmann* et l. 1952) In the series of 149 cases investigated by *Stans-Knudsen* (1960) four were carcinoma in situ cases (2.4.100)

According to *Kleinsasser* (1961 a) undiff rentiated carcinoma accounts for between 30 and 50 per cent of supraglottic carcinomas, whereas in the category of carcinomas of the vocal cords the corresponding figure is as low as 10 per cent. *Portmann* and *Moore* (1942) have stated that the reason for the distinctly poorer prognosis for supraglottic carcinomas as compared to carcinomas of the vocal cords is not solely the dense network of lymph vessels in the supraglott c region and the consequent abundance of metastases but also the greater mal gnancy f anaplastic carcinomas.

Table 13 presents distribution f the cases incl ded in the present material into histological differentiation stages ac ording t the sites of the tumors in different anatomic regions, and Table 14 the hist logical differentiation of the cases according to the clinical stages.

The classification is based on the principles expounded by *Kleinsasser* (1961 a)

The material includes 24 cases f *carcinoma in situ*, and their ratio to the total series is 4.100. Twenty-one of the cases belong to the category of carcinomas of the vocal cords, and three to th t f supraglottic carcinomas.

Thirty per cent of the material (190/638) consists f *well differentiated* cases f carcinoma (Table 15) Among glottic tumors such cases account for 38 per cent of the total (79/207) or proportionally more than in the category of supragl tt l tumors (26 per cent, or 110/430) The differenc between the figures is not, however statistically significant.

Poorly differentiated carcinomas ccount for 47 per cent (303/638) f the material (Table 15) Statistically there is ery high probabil ty that poorly differentiated

TABLE 13

Histology in 638 cases of laryngeal cancer according to site of tumor

Histological differentiation	Total number of cases	Per cent of total number of cases	Supraglottic Cases	Supraglottic Per cent	Glottic Cases	Glottic Per cent	Subglottic Cases
Carcinoma in situ	24	4	3	1	21	10	–
Well differentiated carcinoma	190	30	110	26	79	38	1
Poorly differentiated carcinoma	303	47	216	50	87	42	–
Undifferentiated carcinoma	121	19	101	23	20	10	–
Total	638	100	430	100	207	100	1

TABLE 14

Histology of 638 cases of laryngeal cancer at different clinical stage

Histological differentiation	Total number of cases	Stage I Cases	Stage I Per cent	Stage II Cases	Stage II Per cent	Stage III Cases	Stage III Per cent	Stage IV Cases	Stage IV Per cent
Carcinoma in situ	24	17	13	7	3	–	–	–	–
Well differentiated carcinoma	190	42	31	93	30	42	34	13	18
Poorly differentiated carcinoma	303	59	45	155	50	65	44	36	49
Undifferentiated carcinoma	121	17	13	53	17	27	22	24	33
Total	638	135	100	308	100	122	100	73	100

carcinomas represent the most characteristic histological differentiation stage in the total material. In the supraglottic group, poorly differentiated carcinomas represent 50 per cent of the total number (216/430) or relatively more than in the glottic group 42 per cent (87/207) although the difference is not statistically significant.

Nineteen per cent of the total material (121/638) consists of *undifferentiated cardnoma* (Table 13). Among supraglottic carcinomas, the figure is 23 per cent (101/430) and among glottic carcinomas 10 per cent (20/207). In the supraglottic group, undifferentiated forms occur more frequently than they do in the glottic group ($P < 0.001$).

Comparing the histological differentiation of tumors at various clinical stages (Table 14) the relative number of well differentiated carcinomas may be observed to decrease as the lesion spreads over a wider area (Stage I – Stage IV). Correspondingly the

relative number of undifferentiated carcinomas increases steadily from the first stage to the fourth. No statistically significant difference, however can be noted between the figures.

DISCUSSION

The distribution of the present material into different differentiation stages on the basis of the histological picture presented by the carcinomas deviates to some extent from the figures published in the literature. The chief difference is that only 50 per cent of the cases in the material represent well differentiated carcinomas. Well differentiated types are generally considered to constitute the majority of cases of laryngeal cancer (*Foxen* 1957 *Svane-Knudsen* 1960)

One reason for the small occurrence of well differentiated forms in the present material may be the fact that 67 per cent of the cases in olve supraglottic tumors, among which, as it is well known, well differentiated carcinomas are less common (*Kleinsasser* 1961 a)

The infrequent occurrence f well differentiated carcinomas in the present material signifies that the relative occurrence of less ripe carcinomas is correspondingly more frequent. The relative occurrence of poorly differentiated carcinomas in the material is the greatest (47 per cent) exceeding th t reported in the literature. The relative occurrence of undifferentiated carcinomas in the present material corresponds to the figures cited in the literature (*Portmann* and *Moure* 1942, *Foxen* 1957)

Undifferentiated carcinomas were observed to occur more frequently ($P < 0.01$) in the supraglottic than in the glottic category The proportion of undifferentiated carcinomas in the glottic group (10 per cent) corresponds to the figures reported in the literature. *Kleinsasser* (1961) among others, states that every tenth carcinoma of the vocal cords is of the undifferentiated type.

The relative occurrence of carcinoma in situ forms by and large corresponds to the figures cited in the literature (*Altmann* et al. 1952)

The histological picture of carcinomas was observed to change to some extent as the tumors spread to a wider area. The proportional occurrence of anaplastic carci nomas increased from 15 to 33 per cent as the clinical stage rose from the first to the fourth, but the differences were not statistically significant.

TABLE 13
Histology in 638 cases of laryngeal cancer according to site of tumor

Histological differentiation	Total number of cases	Per cent of total number of cases	Supraglottic Cases	Supraglottic Per cent	Glottic Cases	Glottic Per cent	Subglottic Cases
Carcinoma in situ	24	4	5	1	21	10	–
Well differentiated carcinoma	190	30	110	26	79	38	1
Poorly differentiated carcinoma	303	47	216	50	87	42	–
Undifferentiated carcinoma	121	19	101	23	20	10	–
Total	638	100	430	100	207	100	1

TABLE 14
Histology of 638 cases of laryngeal cancer at different clinical stage

Histological differentiation	Total number of cases	Stage I Cases	Stage I Per cent	Stage II Cases	Stage II Per cent	Stage III Cases	Stage III Per cent	Stage IV Cases	Stage IV Per cent
Carcinoma in situ	24	17	13	7	2	–	–	–	–
Well differentiated carcinoma	190	42	31	93	30	42	34	13	18
Poorly differentiated carcinoma	303	59	44	155	50	53	44	36	49
Undifferentiated carcinoma	121	17	13	53	17	27	22	24	33
Total	638	135	100	308	100	122	100	73	100

carcinomas represent the most characteristic histological differentiation stage in the total material. In the supraglottic group, poorly differentiated carcinomas represent 50 per cent of the total number (216/430) or relatively more than in the glottic group 42 per cent (87/207) although the difference is not statistically significant.

Nineteen per cent of the total material (121/638) consists of *undifferentiated carcinoma* (Table 13). Among supraglottic carcinomas, the figure is 23 per cent (101/430) and among glottic carcinomas 10 per cent (20/207). In the supraglottic group, undifferentiated forms occur more frequently than they do in the glottic group ($P < 0.001$).

Comparing the histological differentiation of tumors at various clinical stages (Table 14), the relative number of well differentiated carcinomas may be observed to decrease as the lesion spreads over a wider area (Stage I – Stage IV). Correspondingly the

In the treatment of primary tumors of the supraglottic region, partial resection — supraglottic laryngectomy — has maintained its firm position. Insofar as it is used in carefully selected cases alone, this procedure gives good results (*Ogura* 1958, 1962, *Leroux-Robert* 1961). *The most important thing to watch for is that the growth has* not spread too near the vocal cords or the posterior portions of the larynx. The arytenoids, *for example* must be completely free of any malignancy. Supraglottic laryngectomy may also be resorted to in cases where the epiglottic tumor has spread to the base of the tongue (*Ogura* 1962).

Ogura (1962) has performed hemilaryngectomy and laryngofissure in supraglottic cases where the lesion is situated in a small area, such as, e.g. one of the ventricular bands.

With regard to all other tumors of the supraglottic region, total laryngectomy is considered imperative (*Pietrantoni* and *Fior* 1958, *Jackson* and *Norris* 1961, *Ogura* 1962).

5. GLOTTIC CANCER

In the treatment of tumors in the vocal cords, two different lines of approach are mainly taken: *surgery or radiotherapy alone*. *Combined surgery and radiotherapy* is less common. The combination is generally used when the malignancy has spread beyond the region of the vocal cords.

In the event of a Stage I growth, equally good results can be achieved either by radiotherapy alone or by laryngofissure (thyrotomy and tumor excision). The cure rates reported in the literature vary between 70 and 95 per cent (*Pietrantoni* and *Fior* 1958, *Kleinsasser* 1961 c, *Smith* et al. 1961, *Lauerma* and *Siirala* 1962, *Bryce* et al. 1963, *Blady* 1965, *Taskinen* and *Holsti* 1966, *Heise* and *Baylis* 1966).

Irradiation exclusively applied has received increasing favor in the treatment of Stage I tumors of the vocal cords. In the comparative phoniatric study carried out by *Ruka* and *Lauerma* (1967), the voices of patients treated by irradiation were ascertained to be statistically significantly better than the voices of patients treated surgically (thyrotomy and tumor excision).

If a tumor remains in the region of the vocal cords but has advanced to Stage II — i.e., the growth is situated in, for instance, both vocal cords — laryngofissure is not considered a sufficiently radical measure (*Leroux Robert* 1956, 1959). If in such cases the movements of the vocal cords are still normal, the results achieved with radiotherapy alone are nearly on a par with those recorded for Stage I cases (*Bryce* et al. 1963, *Heise* and *Baylis* 1966).

If a tumor limited to the region of the vocal cords has caused a distinct obstruction to the movements of one or both of the vocal cords or a complete fixation, *Stane-Knudsen* (1960) and *Ogura* (1962), for example, consider total extirpation of the larynx essential. *Bryce* et al. (1963) recommend radiotherapy alone and extremely close follow-up observation in these cases. Thereby any possible recurrence can be detected in time and treated successfully by surgery.

VII SURGICAL AND RADIOLOGICAL INDICATIONS AND TECHNIQUES

A Survey of literature

1 GENERAL

"Carcinoma of the larynx is a disease which, in favorable regions and in the early stages, can be cured in a quite remarkable percentage of cases" (*Bryce* et al. 1963)

Ogura (1962) among others, states that the results of radiological and surgical treatment are largely dependent on the site of the tumor and the stage it has reached at the time the patient reports for initial treatment.

The importance of the histological differentiation of the tumor from the standpoint of planning therapy is generally rather slight, as it has not been indisputably proven to have any clear significance in the prognosis (*Blümlein* 1957 *Shaw* 1957 *Svane-Knudsen* 1960). Undifferentiated carcinoma was previously treated exclusively by irradiation, for it was considered to be more sensitive to radiotherapy than were more highly differentiated carcinomas (*Leicher* 1963 b) Nowadays, however better results have been obtained by radical, surgical treatment in these cases than by irradiation alone (*Pietrantoni* and *Fior* 1958)

The patients age is no longer a decisive factor in planning treatment, either (*Shaw* 1957) Similarly many patients in weak condition can be strengthened by suitable medical therapy to the point where, for example, a planned surgical operation can be performed (*Pietrantoni* and *Fior* 1958)

2. SUPRAGLOTTIC CANCER

An examination of the literature dealing with the treatment of supraglottic cancer reveals that surgery is most commonly favored (*Shaw* 1957 *Pietrantoni* and *Fior* 1958 *Leroux Robert* 1956, 1961 *Ogura* 1962)

Stage I supraglottic tumors, especially those that are situated on the laryngeal surface of the epiglottis, constitute an exception In these cases, radiotherapy alone has resulted in a five-year-cure rate of better than 70 per cent (*Smith* et al. 1961)

Where irradiation has been exclusively used on other growths in the supraglottic region, the results have not been as favorable as with surgery or with a combination of surgery and radiotherapy Thus, for example *Lederman* (1961) reported having treated with teleradium and telecobalt 174 supraglottic tumors of different types and obtained a five-year-cure rate of 22 per cent.

Opinions vary to some extent as to th kind of cases requiring dissection. *Shaw* (1957), *Pietrantoni* and *Fior* (1958), *Kleinsasser* (1961 c) *Jackson* and *Norris* (1961) and *Ogura* (1962) contend that a radical neck dissection must be performed irrespective of the site of the primary tumor in every case where clinically palpable lymph nodes occur in the neck.

In cases where clinically palpable lymph nodes do not exist, the probability of the occurrence of metastases in the neck can, according to *Pietrantoni et al.* (1962) be estimated on the basis of the following circumstances

1) The site of the primary tumor The possibility of lymph node metastases is greatest in tumors situated in the marginal areas of the larynx (with the exception of the laryngeal surface of the epiglottis) considerable in other supraglottic tumors, less so in subglottic tumors and minimal in growths involving the vocal cords.

2) The anatomico-clinical aspect of the primary tumor Metastases are most frequent in infiltrating, and less numerous in vegetating lesions.

3) The histology of the primary tumor Metastases are most frequent among anaplastic carcinomas.

The authors regard the first consideration, that of the site of the primary tumor as the most important.

According to *Kleinsasser* (1961 c) and *Ogura* (1962) the radical neck dissection may be left unperformed in the cases in the supraglottic category where the growth is situated on the posterior surface f the epiglottis without the presence of palpabl lymph nodes (Stage I) inasmuch as metastasization is rare on account of the sparseness of lymph vessels in this region. In the event a dissection is performed in such cases, it should be done, according to *Pietrantoni* et al. (1962) on both sides because of the central position of the tumor. *Ogura* (1962) does not recommend radical neck dissection in cases where the tumor is situated in on or the other of the ventricular bands and/ or the anterior commissure (without palpable nodes) but considers it imperative in cases where the epiglotti growth has extended into the base f the tongue. According to *Kleinsasser* (1961 c) the danger of metastases is exceedingly great in cases where the tumor has affected the arytenoid, and in such cases the neck dissection should be ultraradical"

If lesion in the glottic category is situated strictly in the region of the vocal cords, a radical neck dissection is considered necessary only in cases where palpable lymph nodes are present in the neck (*Leroux Robert* 1961, *Ogura* 1962, *Pietrantoni* et al. 1962).

Where a tumor of the vocal cords has extended even to the lightest degree into the supraglottic or subglottic areas, *Pietrantoni* and *Fior* (1958) for example, feel that a radical neck dissection is necessary *Kleinsasser* (1961 c) does not perform a dissection if the glottic tumor has spread from the anterior commissure into the ventricular bands, but he undertakes the operation invariably if the spread has involved the posterior parts of the larynx, notably the arytenoid.

In the treatment of subglottic tumors (as well as glottic carcinomas that have extended to the subglottis) radical neck dissection is nowadays considered mandatory (*Ogura* 1962, *Pietrantoni* et al. 1962). Particular attention in the performance of this operation should be paid to peritracheal and recurrent glands (*Pietrantoni* et al. 1962).

In the event a glottic growth has spread beyond the glottic region, total removal of the larynx is regarded as imperative (*Kleinsasser* 1961 c, *Ogura* 1962) *Ogura* (1962) considers the prognosis of a tumor that has spread to the subglottis, in especial, to be poor and for this reason he greatly favors radical measures.

4 SUBGLOTTIC CANCER

Since carcinomas occurring in the subglottic region alone are rather seldom met with, sufficient statistical data are not available regarding the results obtained through different forms of therapy According to *Leicher* (1963 b) depending on the extent of the tumor, the five-year-cure rate in such cases is 40 to 45 per cent.

Radiotherapy alone can be applied, according to *Leicher* (1963 b) only in cases where the subglottic tumor is situated in the anterior part of the subglottic region. The irradiation must then be extended to the area of the paratracheal lymphatics in order to prevent metastases.

In the case of other tumors of the subglottic region, total extirpation of the larynx is considered imperative (*Leroux Robert* 1956, *Ogura* 1962, *Pietrantoni* et al 1962, *Leicher* 1963 b)

5 CERVICAL LYMPH NODE METASTASES

In 1958 *Pietrantoni* and *Fior* published a report on the good results they had achieved in the surgical treatment of Stage II supraglottic cancer To the removal of the primary tumor (total laryngectomy) they had added radical dissection of one or both sides of the neck and thereby obtained considerably better therapeutic results than by limiting the operation to the primary malignancy They performed dissections as an elective" measure — i.e., they performed it even in cases where no clinically palpable lymph nodes occurred in the neck. In their paper they "emphasized that clinically impalpable metastases are very frequent in hypopharyngeal and in extensive supraglottic tumours and therefore serious consideration should be given to elective neck dissection in all these cases."

Instead of this elective neck dissection, *Leroux Robert* (1956, 1959) used systematic postoperative radiotherapy in the treatment of supraglottic tumors and achieved practically as good results as those reported by *Pietrantoni* and *Fior* (1958) *Pietrantoni* and *Fior* (1958) expressed the view that the results obtained with postoperative radiotherapy applied in lieu of radical neck dissection largely depend on the attending radiologists, radiological establishments and equipment.

The literature published in recent years makes it evident that the use of radical neck dissection has made headway in different parts of the world.

B Therapeutic methods used in the present material

During the years between 1949 and 1959 the f llowing surgical and radiation methods of treatment were used at the Otolaryngol gical and the Radiological Hospitals in Helsinki in cases of laryngeal cancer

Thyrotomy and excision of the tumo
Horizontal, supraglottic laryngectomy
Total laryngectomy
Radical neck dissection
Lymph node extirpation
X-ray therapy alone
Postoperative X ray therapy

Table 15 shows to what extent each of the foregoing methods of therapy were used t these hospitals.

TABLE 15
Methods f treatment in 638 cases f laryngeal cancer

Method	Number of cases	Incidence of total number per cent
Thyrotomy and tumor excision	35	5.5
Supraglottic laryngectomy	6	0.9
Total laryngectomy	47	7.4
Total, surgery alone	*(88)*	*(13.8)*
Thyrotomy and tumor excision + X ray	56	8.7
Supraglottic laryngectomy + X ray	15	2.3
Supraglottic laryngectom + lymph node extirpation + X-ray	7	1.1
Supraglottic laryngectomy + radical neck dissection + X ray	12	1.9
Total laryngectomy + X-ray	83	13.0
Total laryngectomy + lymph node extirpation + X-ray	40	6.3
Total laryngectomy + radical neck dissection + X-ray	12	1.9
Total, surgery + X-ray	*(225)*	*(35.2)*
Total, X-ray alone	*(3 5)*	*(51.0)*
Total	638	100 0

The applications of the different methods of treatment in th present material are described in the following

In o... ... was the histological structure of the tumor considered to be a deci... f... ...ing the mode of treatment. If the tumor was found to be exceeding ... ed the patient could be treated with primary irradiation, reg...es ... xtent of the lesion. In the following table (Table 21), the cases t... h... d... ...ay therapy alone have been classified according to the anatomic site ... of the lesion.

Foucdar ... *ca* (1962) have described the method of X ray therapy used als... in th... ...resent material. "In roentgen therapy the factors were as follows: 19... ...n 1.0 mm Cu, 60 cm sourceskin distance and H. V. L. 1.5 mm

TABLE 21

325 case... ...by X ray therapy alone according to anatomic site extend and clinical stage

Sta...	T.N.M.	Number of cases
	Supraglottic cancer	
I	T N_0M_0	35
II	$T_2N_0M_0$	74
	$T_3N_0M_0$	39
	$T_4N_0M_0$	
III	T N M_0	1
	T_2N M_0	11
	$T_3N_1M_0$	18
IV	$T_4N_1M_0$	1
	T_1N_2M	2
	$T_2N_2M_0$	7
	T_3N M_0	11
	$T_4N_2M_0$	1
	T_2 ... M_1	2
	... M_1	2
Total supraglottic cases		*(211)*
	Glottic ca...c...	
I	T_1N M	65
II	T N M	23
	T_2N M	17
III	$T_1N_1M_0$	5
	...	1
	...	4
[illegible]		*(113)*
	...glottic ...	
I	...	1
		325

Co. Two therapeutic fields, according to the extent of the tumour and the possible metastases, were 4 × 4 6 × 6, 6 × 8 and 8 × 10 cm, and if necessary one additional field anterior When recurrences or metastases in the neck were involved *the posterior fields were also treated bilaterally The principles previously introduced* by *Mustakallio* (1944) were followed in the therapy The daily dose was 260 r for the posterior fields 300 r measured by skin area. If severe dyspnoea was present treatment was started with doses of 100–150 r and gradually increased. The total dosage was 5 000–6 000 r on the tumour and with a daily dose 260 r treatment usually lasted 28 days. Additional fields were used in the treatment of the metastases if required.

7 POSTOPERATIVE X RAY THERAPY

Postoperative X ray therapy was given in 71.7 per cent (225/315) of the surgery cases.

Postoperative radiotherapy was administered in all the clinical stages of the supraglottic and glottic groups, and the ratio of the number of patients receiving postoperative radiotherapy to those not so treated increased as the extent of the malignancy grew larger A second criterion f r the administration of postoperativ X ray therapy was suspected or observed metastases in the lymph nodes of the neck. If malignant tissue was detected in the lymph nodes, X-ray therapy was gi en from three fields, and in bilateral metastases from four

The same method f X ray therapy was applied in postoperativ treatment as in primary X ray therapy (p. 00)

C. Discussion on modes of treatment

If we compare the indications for therapeutic procedures used in the material with the indications described in the literature we shall observe that there are certain disparities.

The indications for thyrotomy and extirpation of the tumor are generally much more limited than in the present material. For instance, *Ogura* (1962) states that thyrotomy (laryngofissure) can be used only in the treatment of Stage I carcinoma of the vocal cords and, in addition, of cases in which the tumor involves a small area of one f the ventricular bands. Of lat years thyrotomy has been little used in the treatment of Stage I tumors in the vocal cords, for th results obtained by means of radiotherapy alone have been equally good (*Pietrantoni* and *Fior* 1958, *Kleinsasser* 1961 c, *Hesse* and *Baylis* 1966, among others) and the function of the larynx has been observed to be better preserved following radiotherapy than after surgery (*Rukka* and *Lauerma* 1967).

Horizontal, supraglottic laryngectomy has been used rather little in the series t hand (40 cases). The indications for it correspond to those presented in the literature

(*Ogura* 1958, 1962, *Leroux Robert* 1961) *Ogura* (1963) performs this operation even in cases where an epiglottic tumor has spread to the base of the tongue. Corresponding cases in the present material number six.

Total laryngectomy has been the commonest operation in the present series (182 cases) and the indications correspond to those reported in the literature (*Jackson* and *Norris* 1961)

Over half the cases in the material were treated by X ray therapy alone (325/638). The number is large considering that 67 per cent of the cases involve supraglottic tumors. Treating supraglottic tumors exclusively by irradiation is not generally recommended except in Stage I cases, especially when the malignancy involves the posterior surface of the epiglottis (*Shaw* 1957 *Leicher* 1963 b) The administration of radiotherapy alone in Stage I cases of tumors in the vocal cords is generally approved (*Smith* et al. 1961 *Lauerma* and *Surola* 1962, *Taskinen* and *Holsti* 1966) and in the present material, too, it has been the most frequently used treatment in such cases.

Postoperative irradiation was used in 71 7 per cent of the surgical cases. Irradiation was considered to ensure the results of the surgery and this agrees with, for example the view expressed by *Leicher* (1961 1963 b)

Few measures were taken toward the treatment of metastases of the lymph nodes of the neck included in this material Postoperative radiotherapy appears to have been significant in the prevention of lymph node metastases. The smallness of the number of radical neck dissections is explained by the fact that the material dates from precisely those years (1949—1959) when dissection was only making its breakthrough as a therapeutic measure The extirpation of individual lymph nodes in lieu of dissection is no longer favored (*Leicher* et al. 1956, *Leicher* 1963 b)

VIII RESULTS

A Results according to age and sex

Reports on the extent to which the age of laryngeal cancer patients has a bearing on the prognosis vary considerably in the literature

According to *Howie* (1948) the prognosis for patients under 40 years of age is poorer than for patients over 40 *Negus* (1948) for his part, contends that the prognosis does not depend on the patient's age In the material of *Fendel* et al. (1963) consisting of 588 cases, the prognosis for patients over 60 years of age was to a high degree of probability "mit hoher Wahrscheinlichkeit" poorer than for patients under 60.

According to *Pietrantoni* and *Fior* (1958) there was no difference between the sexes in the clinical behavior of cancer of the larynx. *Kirchner* and *Malkin* (1953) *Scane-Knudsen* (1960) and many other investigators consider the prognosis for women better than for men.

As previously noted (p. 24), the average age of the patients comprising the material is 55.7 years. Thirty-one per cent were under 51 and 69 per cent over 51 years of age.

The results of treatment according to age are presented in Table 22.

All four patients under the age of 31 have been free of symptoms for more than five years following the termination of therapy The cure rate is thus 100 per cent, but because of the small number of cases in this age group the result is not statistically

TABLE 22
Five-year results in 638 cases of laryngeal cancer according to age

Age in years	Total number of cases	Number of determinant cases	Symptomless after 5 years Cases	Per cent	Recurrence within 5 years Cases	Per cent
0–30	4	4	4	100	–	–
31–40	48	46	29	63	17	37
41–50	148	136	81	60	55	40
Total under 51 years	*(200)*	*(186)*	*(114)*	*(61)*	*(72)*	*(39)*
51–60	223	201	105	52	96	48
61–70	164	143	65	45	78	55
71–80	50	44	19	43	25	57
81–90	1	1	–	–	1	–
Total over 51 years	*(438)*	*(389)*	*(189)*	*(49)*	*(200)*	*(51)*
Total	638	575	303	53	272	47

significant and not comparable with those registered for the other groups. The cure rate is next highest in the group consisting of patients between the ages of 31 and 40 (65 per cent) and it diminishes evenly as the groups grow older Between the five-year results for the age group 31–40 and the age group 71–80 there is a difference of 20 per cent, which is statistically significant ($P < 0.01$)

Table 23 shows the extent to which the patients age has affected the therapeutic results in the *supraglottic* group

TABLE 23.
Five-year results in 430 cases of supraglottic cancer according to age

Age in years	Total number of cases	Number of determinant cases	Symptomless after 5 years: Cases	Per cent	Recurrence within 5 years: Cases	Per cent
0–30	–	–	–	–	–	–
31–40	35	33	19	58	14	42
41–50	123	115	64	55	51	45
Total under 51 years	*(158)*	*(148)*	*(83)*	*(56)*	*(65)*	*(44)*
51–60	145	133	58	44	75	56
61–70	96	86	28	33	58	66
71–80	51	28	6	21	22	79
81–90	–	–	–	–	–	–
Total over 51 years	*(27)*	*(247)*	*(9)*	*(3)*	*(155)*	*(63)*
Total	430	395	175	45	220	55

Studying the results, we should note that taking into account all the determinant supraglottic cases, the cure rate for the patients under 51 is 56 per cent (83/148) and for the patients over 51 years of age 37 per cent (92/247) (Table 23) The therapeutic result for the age groups under 51 is from the statistical standpoint to a highly significant degree better than for those over 51 ($P < 0.001$)

To make sure of this difference, the $T_2N_0M_0$ cases were separated from the supraglottic group (Table 24) With respect to site and extent of the primary lesion, these cases are homogeneous and their number (110) is relatively large and offers some possibilities for the statistical estimations

TABLE 24
Five-year results in 110 cases of supraglottic cancer (Stage II $T_2N_0M_0$) according to age

Age	Number of determinant cases	Symptomless after 5 years: Cases	Per cent	Recurrence within 5 years: Cases	Per cent
Under 51 years	38	29	76	9	24
Over 51 years	72	31	43	41	57
Total	110	60	54	50	46

In Table 24 the percentage of cures among the patients under 51 years of age (76 per cent) is statistically significantly higher than among those over 51 (43 per cent) ($P < 0.01$).

The results of treatment for *glottic* tumors are classified according to age in Table 25.

TABLE 25.
Five-year results in 207 cases of glottic cancer according to age

Age in years	Total number of cases	Number of determinant cases	Symptomless after 5 years Cases	Per cent	Recurrence within 5 years Cases	Per cent
0–30	4	4	4	100	–	–
31–40	13	13	10	77	3	23
41–50	23	21	17	81	4	19
51–60	77	67	46	69	21	31
Total under 61 years	*(119)*	*(105)*	*(77)*	*(73)*	*(28)*	*(27)*
61–70	68	57	37	65	20	35
71–80	19	16	13	81	3	19
81–90	1	1	–	–	1	100
Total over 61 years	*(88)*	*(74)*	*(50)*	*(68)*	*(24)*	*(32)*
Total	207	179	127	71	52	29

In Table 25 there are so few patients under the age of 51 in the glottic group that no reliable statistical study of the possible effect of age on the results of treatment can be made, as was done in the group of supraglottic cases. For this reason, the glottic group has been divided into patients under 61 and those over 61 years of age. *No statistically significant difference between the rates of cure for these two sub-groups can be observed.*

It has previously (p. 24) been remarked that the average age of the 23 female patients upon admission to hospital was 44.4 years and that of the male patients 56.1 years. The number of determinant cases in the women's group was 21 of which 15 were symptomless five years after the termination of treatment. The cure rate was thus 71 per cent. The corresponding cure rate for the men was 52 per cent. The difference seems great, but because of the small number of women involved, it is not statistically significant.

DISCUSSION

The effect of the age of patients on the end results of treatment has been investigated in the literature. The conclusions reached by different investigators vary.

The present material yielded results deviating from the views of *Howie* (1948) and Negus (1948) reported on page 49. But the results agree with those reported by *Fendel* et al. (1965).

Accordingly throughout the entire material, the prognosis proved to be consistently better for younger than for older patients. In addition, considering the supraglottic and glottic groups separately it was observed that among the former the prognosis for patients under 51 years of age was better than for those over 51 whereas in the glottic group such a difference was not established.

The women's superior five-year-cure rate suggests that the prognosis for women with this disease may be better than for men. The number of women in the material is so small, however that the result is not statistically significant. *Kirchner* and *Malkin* (1953) and *Svane Knudsen* (1960) among others, regard the prognosis for women to be better than for men.

B Results according to anatomic site extent and clinical stage

One of the central questions dealt with in the literature on laryngeal cancer is the dependence of the end results of treatment on the site and extent of the lesion in the larynx. Closely associated with this question is the matter of the varying tendency of tumors situated in different anatomic regions to metastasize into the lymph nodes and the effect of metastases on the results.

According to *Ogura* (1955) the metastasization of a tumor into the neck depends principally on the location of the lesion in the larynx and to a lesser degree on its extent or its histological differentiation (degree of anaplasia) In the event cervical metastases are present on admission of the patient to the hospital his chances of surviving are far slimmer than in the absence of metastases. *Smith* et al. (1961) observed that when metastatic nodes were present in the neck before treatment was started, the five-year-cure rate fell to approximately 40 per cent even in the cases involving a T_1 type of primary lesion.

If the primary lesion is situated in the supraglottic region the therapeutic results according to various reports are distinctly poorer than if the tumor is located in the region of the vocal cords (*Pietrantoni* and *Fior* 1958, *Leroux Robert* 1959). The most important reason for this inferior prognosis is believed to be the great tendency of supraglottic tumors to spread to the lymph nodes in the neck Attention has been drawn to this circumstance by numerous investigators (*Smith* et al 1961 *Ogura* 1962, *Pietrantoni* et al. 1962)

If a supraglottic tumor has originated in the posterior parts of the larynx, notably the arytenoid, or spread there the prognosis is poor because of its great tendency to metastasize *Kleinsasser* (1961 c) stated that if the lesion has affected the region of the arytenoids, the prognosis for the patient is exceedingly poor

Nevertheless, it has been observed in a number of investigations that even in the supraglottic region there are certain types of tumors in the treatment of which very good results have been achieved For example, in the treatment of Stage I tumors situated on the posterior surface of the epiglottis, nearly as good results have been obtained as in the treatment of malignancies of the corresponding stage in the vocal cords (*Pietrantoni* and *Fior* 1958 *Norris* 1959 *Smith* et al. 1961) The good prognosis

for these tumors is due, according to *Kleinsasser* (1961 c) to a large extent to the fact that the network of lymph vessels on the laryngeal surface of the epiglottis is sparse and therefore they are not very sensitive to metastatization.

The five-year-cure rate for patients with Stage I cancer of the vocal cords is well known to be extremely good (*Smith* et al. 1961 *Lauerma* and *Sirala* 1962, *Hesse* and *Berlis* 1966 *Taskinen* and *Holsti* 1966)

In the treatment of Stage II tumors of the vocal cords, end results comparable to those obtained with the Stage I group are possible provided the mobility of the vocal cords remains normal. If the mobility of the vocal cords has become impaired or the lesion has caused a fixation there, the prognosis worsens considerably compared to the preceding groups For this reason, *Hesse* and *Berlis* (1966) divide the tumors of the vocal cords in group T of the T.N.M. system into two categories. The one category includes the cases in which the motility of the vocal cords is normal and the other the cases in which the lesion has caused impairment of the motility or a fixation of one or both vocal cords. The authors recommend including the first category among Stage I cases.

One reason for the good results achieved in treating tumors of the vocal cords is that such tumors grow slowly and another reason is that in the region of the vocal cords lymph vessels are present very sparsely (*Svane-Knudsen* 1960) Therefore, the metastasization of tumors situated in the region of the vocal cords alone into the lymph nodes of the neck is extremely rare (*Link* 1962) *Kuhn* et al. (1957) report that metastases occur in 0.8 per cent of the cases of tumors in the vocal cords.

The cure rates for laryngeal cancer steadily deteriorate from the first to the fourth clinical stage. The figures given by *Smith* et al. (1961) for example, are as follows Stage I = 91 per cent, Stage II = 72 per cent, Stage III = 45 per cent and Stage IV = 22 per cent.

Table 26 presents the *five-year-cure rates for the total material* classified according to the T.N.M. system and the clinical stages.

Of all the determinant cases in the material. 53 per cent (303/575) remained symptomless five years after the termination of treatment (Table 26) The best results were obtained in the cases of *Stage I* tumors (85 per cent) The results achieved at this stage are better ($P < 0.01$) than those scored *for the other stages* (Stages *II* = 49 per cent. Stage *III* = 46 per cent, Stage IV = *21* per cent)

The end results of treatment of the *Stage II* and *Stage III* cases are approximately the same, or 49 per cent and 46 per cent, respectively According to the clinical staging, metastatic lymph nodes were not clinically suspected to be present in any of the Stage II cases (N_0) whereas in Stage III cases their presence was observed (*N*)

In *Stage IV* cases, the five-year survival rate is 21 per cent (14/66) The best therapeutic result (5/9) was obtained in group $T N_1 M_0$ in which the lesion had already spread outside the larynx but palpable lymph nodes occurred only on one side of the neck and were mobile. In group $T_3 N_3 M_0$ the end results of treatment were 32 per cent (7/19) In this group the tumor was still located in a single anatomic region and clinically suspected metastatic lymph nodes were fixed in the neck. Of the remaining

TABLE 26.
Five-year results in 638 cases of laryngeal cancer according to T.N.M. system and clinical stage

Stage	T.N.M.	Total number of cases	Number of determinant cases	Symptomless after 5 years Cases	Symptomless after 5 years Per cent	Recurrence within 5 years Cases	Recurrence within 5 years Per cent
I	$T_1N_0M_0$	155	124	106	85	18	1
II	$T_2N_0M_0$	160	139	76	55	63	45
	$T_3N_0M_0$	124	107	49	46	58	54
	$T_4N_0M_0$	24	24	6	25	18	75
Total, Stage II		*(308)*	*(270)*	*(131)*	*(49)*	*(139)*	*(51)*
III	$T_1N_1M_0$	15	15	11	74	4	26
	$T_2N\ M_0$	45	42	21	50	21	50
	$T_3N_1M_0$	62	58	20	35	33	65
Total, Stage III		*(122)*	*(115)*	*(52)*	*(46)*	*(61)*	*(54)*
IV	$T\ N\ M_0$	11	9	5	–	4	–
	$T_1N_2M_0$	3	2	–	–	2	–
	$T_2N_2M_0$	21	19	7	–	12	–
	$T_3N_2M_0$	21	19	1	–	18	–
	$T\ N_2M_0$	13	13	1	–	12	–
	$T_3N_0M_1$	2	2	–	–	2	–
	T_3N_0M	2	2	–	–	2	–
Total, Stage IV		*(73)*	*(66)*	*(14)*	*(21)*	*(52)*	*(79)*
Total		638	575	303	53	272	49

38 Stage IV cases, only two were symptomless after five years following the termination of treatment (5 per cent)

In the *Stage II* and *Stage III* cases, the cure rates worsen progressively as the extent of the involvement increases. In the Stage II cases, $T_2N_0M_0$ = 55 per cent, $T_3N_0M_0$ = 46 per cent and $T\ N_0M_0$ = 25 per cent while in the Stage III cases, $T_1N_1M_0$ = 74 per cent, $T_2N_1M_0$ = 50 per cent and T_3N_1M = 35 per cent.

The five-year results obtained in the *supraglottic* group are presented in Table 27

Seventy per cent (30/43) of the *Stage I* cases of *supraglottic* cancer were cured (Table 27) This result is better ($P < 0.01$) than the therapeutic results for supraglottic tumors of the *Stage II* (46 per cent) *Stage III* (47 per cent) and *Stage IV* (21 per cent)

In 32 cases the *Stage I supraglottic* tumor was situated in a limited area of the laryngeal surface of the epiglottis, and in this group the rate of survival was 66 per cent (21/32) In nine cases the tumor was situated in the ventricular band and seven of them were cured (7/9) In two cases the tumor involved one of the arytenoids, and both cases remained symptomless more than five years after the termination of treatment.

TABLE 27

Five-year results in 430 cases of supraglotti cancer according to T N M system and clinical stage

Stage	T.N.M.	Total number f cases	Number of determinant cases	Symptomless fter 5 years Cases	Symptomless fter 5 years Per cent	Recurrence within 5 years Cases	Recurrence within 5 years Per cent
I	TN_0M_0	45	45	30	70	15	30
II	$T_2N_0M_0$	123	110	60	55	50	45
	$T_3N_0M_0$	64	55	20	36	35	64
	$T N_0M_0$	23	23	6	26	17	74
Total, Stage II		*(210)*	*(188)*	*(86)*	*(46)*	*(102)*	*(54)*
III	$T_1N_1M_0$	12	12	8	67	4	33
	$T_2N M_0$	42	39	20	51	19	49
	$T N M_0$	49	47	1	36	30	64
Total, Stage III		*(103)*	*(98)*	*(45)*	*(47)*	*(53)*	*(53)*
IV	$T_4N_1M_0$	10	9	5	–	4	–
	$T_1N_2M_0$	5	2	–	–	2	–
	$T_2N_2M_0$	21	19	7	–	12	–
	$T_3N_2M_0$	21	19	1	–	18	–
	$T_4N_3M_0$	13	13	1	–	12	–
	T_2N_0M	2	2	–	–	2	–
	T_3N_0M	2	2	–	–	2	–
Total, Stage IV		*(72)*	*(66)*	*(14)*	*(21)*	*(52)*	*(79)*
Total		430	395	175	45	220	55

The cure rate was nearly as good in the twelve cases of T tumors where the lymph nodes were palpable and which thus belong to *Stage III* Of these eight patients were cured.

In *Stage II* cases of th *supraglotti* group the prognosis ppears to worsen as the lesion spreads to a more extensive area ($T_2N_0M_0$ = 55 per cent. $T_3N_0M_0$ = 36 per cent and $T_4N_0M_0$ = 26 per cent) The differences between the therapeutic results for the T and T_3 groups and, correspondingly the T_3 and T groups are statistically almost significant ($P < 0.025$)

The cure rate lso among *Stage III* cases in the *supraglottic* group worsens as the extent of the lesion increases (T_1 = 67 per cent, T_2 = 51 per cent and T = 36 per cent) but on account of th small number of cases, the differences are not statistically significant.

Table 28 presents the results of treatment in cases of *glottic* tumors classified according to T.N.M. system and clinical stage.

Stage I cases (T ble 28) represent a highly fa orable survival rate (94 per cent, 75/80). The results f treatment are better than in th *Stage II* (55 per cent) and *Stage III* (41 per cent) groups ($P < 0.001$)

TABLE 28.

Five-year results in 207 cases of glottic cancer according to T.N.M. system and clinical stage

Stage	T.N.M.	Total number of cases	Number of determinant cases	Symptomless after 5 years Cases	Per cent	Recurrence within 5 years Cases	Per cent
I	$T_1N_0M_0$	89	80	75	94	5	6
II	$T_2N_0M_0$	37	29	16	55	13	45
	$T_3N_0M_0$	60	52	29	56	23	44
	$T_1N_0M_0$	1	1	–	–	1	–
Total, Stage II		*(98)*	*(82)*	*(45)*	*(55)*	*(37)*	*(45)*
III	$T_1N_1M_0$		3	3	–	–	–
	$T_2N_1M_0$	3	3	1	–	2	–
	$T_3N_1M_0$	15	11	3	–	8	–
Total, Stage III		*(19)*	*(17)*	*(7)*	*(41)*	*(10)*	*(59)*
IV	$T_4N_0M_0$	1	–	–	–	–	–
Total		207	179	127	71	52	29

In the *Stage II* $T_2N_0M_0$ and $T_3N_0M_0$ groups, the cure rates are practically the same (55 per cent and 56 per cent, respectively) while in the other groups of the T-classification there are too few cases to justify any statistical estimation.

Among *Stage II glottic* cancers, the $T_2N_0M_0$ group includes altogether 29 determinant cases and, considered as a single group, their five-year-cure rate is 55 per cent (16/29) In all these cases, the tumor was still totally confined to th region of the vocal cords. In eleven cases, the motility of the vocal cords remained normal, while in 18 cases it had considerably deteriorated or wholly gone The primary cure for the former group was 82 per cent (9/11) and for the latter 39 per cent (7/18)

The total end results for *Stage III* glottic carcinomas are 41 per cent (7/17) The greatest rate of recurrences (8/11) is in group $T_3N_1M_0$, where the lesion had spread outside the region of the vocal cords.

Comparing the therapeutic results for *supraglottic* cancers and for *glottic* cancers (Table 27 and 28) it will be observed th t the salvage rate for *Stage I* cases in the *supraglottic* group (70 per cent) is poorer than the rate (94 per cent) for the *glottic* group ($P < 0.01$)

Among *Stage II* cases, there is no statistically significant difference between the cure rates for *supraglottic* and *glottic* carcinomas. In both groups the survival among $T_2N_0M_0$ cases is precisely the same (55 per cent) Among $T_3N_0M_0$ cases, the treatment of *glottic* tumors yielded a better salvage rate (56 per cent ersus 58 per cent)

Among *Stage III* cases, no appreciable difference between the *supraglottic* and *glottic* groups could be found, either

The *Stage IV* cases belong, with one exception, wholly in the *supraglottic* group, which means that no comparisons can be mad between it and the *glottic* group.

The material includes one subglottic tumor which has been described in the foregoing on p 30

The five-year-cure rate for the entire material (53 per cent) is approximately the same as that reported in the literature by several investigators (*Pietrantoni* and *Fior* 1958, *Glanzinger* 1959 *Smith* et al 1961 *Hesse* and *Baylis* 1966 *Taskinen* and *Holsti* 1966)

In the category of *Stage I* tumors, the five-year salvage rate (8 per cent, 10(121) is rather good. The group includes the most favorable cases, judged from the standpoint of therapy Among them might be mentioned for example 17 d termina t cases of carcinoma in situ (glottic Stage I) which without exception have been symptomless for more than five years following the discontinuation of treatment In addition, the group includes 63 other early-stage tumors of the vocal cords, the cure rates of which are known to be good (*Pietrantoni* and *Fior* 1958, *Smith* et al 1961 *Lauerma* and *Surala* 1962 *Bryce* et al. 1965, *Taskinen* and *Holsti* 1966 *Hesse* and *Baylis* 1966)

Besides the ones mentioned, the group includes tumors situated in a small area of the supraglottis, especially the laryngeal surface of the epiglottis.

A statistically significant difference was observed between the cure rates for Stage I supraglottic and glottic carcinomas. For this reason, it is not possible in the light of the results obtained with the present material to agree with the view expressed by *Smith* et al. (1961) that these tumors should be combined in the same group in calculating survival.

Classified according to extent (T) the Stage II lesions were observed to have an appreciably poorer cure rate than the ones reported in the literature (T = 55 per cent, T = 46 per cent, T_4 = 25 per cent) *Smith* et al. (1961) presented the following figures yielded by their material T = 85 per cent, T_2 = 72 per cent and T = 60 per cent. In the present material, results comparable to those in the study just referred to were obtained only in the treatment of the eleven cases of glottic tumor in the T N_0M_0 group in which the motility of the vocal cords remained normal (82 per cent) In the group of patients whose vocal cords had become impaired or lost motility the salvage rate was only 59 per cent.

The results obtained in the treatment of Stage III cases (46 per cent for the total material) correspond roughly to the cure rates reported in the literature (e.g. *Smith* et al. 1961 45 per cent, *Hesse* and *Baylis* 1966, 52 per cent) The good result obtained in the T N M_0 group, taken as a whole and also in the supraglottic group (67 per cent) raises the doubt that the slight suspected metastases present in the lymph nodes of these patients may not in all cases have been metastases. They may have represented inflammatory changes, for example that quite commonly are noted in lymph nodes as consequence of bad teeth. Histological investigations of the lymph nodes have been made in rather few of these cases, for they have to a large extent been treated by X-ray therapy alone.

The results obtained in the treatment of Stage IV lesions agree with the figures cited in the literature The cure rates for lesions that have spread to this extent and most frequently already metastasized are generally considered poor (*Pietrantoni* and *Fior* 1958 *Bryce* et al. 1963 *Taskinen* and *Holsti* 1966)

In the light of the results obtained with the present material, we may concur in the generally accepted view that the prognosis for supraglottic tumors is poorer than for glottic tumors (*Pietrantoni* and *Fior* 1958 *Leroux Robert* 1959)

C Results according to histology

In 1919 *Bartalena* contended that it is dangerous to take the histological differentiation stages of laryngeal cancer as the sole basis for prognosis, as had been done in using *Broders'* (1920 1926) malignogram, because both ripe and less ripe tissue is apt to occur side by side in different parts of a tumor Similar opinions have been expressed by several other researchers (*Meurman* 1936 a *Harris* and *Klemperer* 1938, *Kirchner* and *Malkin* 1955 *Multanen* 1958 *Norris* 1959 *Kleinsasser* 1961 a)

In the opinion of most researchers, the site, extent and infiltrative growth character of a tumor determine the prognosis for a patient to a higher degree than the histological differentiation stage of the tumor (e.g., *Clerf* et al. 1948, *Bartalena* 1919 *Blümlein* 1957)

Deviating from the foregoing however is the general idea that an undifferentiated carcinoma metastasizes fairly early and has a poor prognosis (*Leicher* 1962 *Kleinsasser* 1961 a)

According to *Kleinsasser* (1961 a) undifferentiated forms account for from 30 to 50 per cent of the tumors in the supraglottic group and about 10 per cent in the glottic group On this basis, he explains that the reason for the poorer prognosis for supraglottic tumors lies not only in the dense network of lymph vessels but also the metastases induced by the anaplastic nature of the carcinoma The same view has also been presented by *Ormerod* and *Shaw* (1956) as well as by *Shaw* (1965)

Table 29 presents five-year-cure rates classified according to the histology of the lesions.

TABLE 29
Five-year results in 638 cases of laryngeal cancer according to histology

Histological differentiation	Total number of cases	Number of determinant cases	Symptomless after 5 years Cases	Per cent	Recurrence within 5 years Cases	Per cent
Carcinoma in situ	24	24	24	100	–	–
Well differentiated carcinoma	190	176	104	59	72	41
Poorly differentiated carcinoma	303	261	125	48	136	52
Undifferentiated carcinoma	121	114	50	44	64	56
Total	638	575	303	5.	272	4

All 24 carcinoma in situ cases in the material have been symptomless for five years following the termination of therapy

Classification of the rest of the material in accordance with the stage of differentiation brings out the fact that the highest rate of cure (59 per cent) in the group of *well differentiated* carcinomas and that the end results grow poorer as the tumors become more anaplastic (*poorly differentiated* = 48 per cent and *undifferentiated* = 44 per cent) The differences between the survival rates are not, however statistically significant.

In Tables 50 and 51 the results of *supraglottic* and *glottic* tumors are given separately according to their histology

TABLE 50.

Five-year results in 430 cases of supraglottic cancer according to histology

Histological differentiation	Total number of cases	Number of determinant cases	Symptomless after 5 years Cases	Per cent	Recurrence within 5 years Cases	Per cent
Carcinoma in situ	3	3	3	–	–	–
Well differentiated carcinoma	110	105	63	52	50	48
Poorly differentiated carcinoma	216	192	78	40	114	60
Undifferentiated carcinoma	101	95	39	41	56	59
Total	430	393	175	45	220	55

TABLE 51

Five-year results in 207 cases of glottic cancer according to histology

Histological differentiation	Total number of cases	Number of determinant cases	Symptomless after 5 years Cases	Per cent	Recurrence within 5 years Cases	Per cent
Carcinoma in situ	21	21	21	100	–	–
Well differentiated carcinoma	79	70	48	69	22	31
Poorly differentiated carcinoma	67	60	4[illegible]	63	22	3[illegible]
Undifferentiated carcinoma	20	19	11	58	8	42
Total	207	179	127	71	52	29

In the total groups of *supraglottic* and *glottic* tumors, the rate of cure of well differentiated carcinomas appears to be slightly higher than that of more anaplastic forms, though no statistically significant difference exist between them

DISCUSSION

All 21 carcinoma in situ cases in the material have been symptomless for more than five years. In the light of the end results, the prognosis for such cases appears to be extremely good. The same conclusion has been reached by among others, *Altmann* et al (1952) and *Kleinsasser* and *Heck* (1959)

When the rest of the material was classified according to histological differentiation, it was observed that the rate of cure declined as the tumor became more anaplastic, though the differences between the various stages of differentiation did not prove statistically significant. Accordingly the stage of histological differentiation was not observed to have any distinct effect on the prognosis for carcinomas. The same results have been reached by for example *Blumlein* (1957) and *Svane-Knudsen* (1960) No clear effect on the prognosis appeared to stem from the differentiation stages of the carcinomas even in cases where the lesions were classified, on the basis of their location, into supraglottic and glottic tumors.

D Results according to mode of treatment

The survey of the literature dealing with therapy and the results of treatment is presented as a whole at the beginning of Chapter VII for it is difficult to separate the literature on indications from that on the end results of treatment. In connection with the discussion contained in the present chapter the reader is referred to the review of literature in Chapter VII.

The rates of cure for five-year periods achieved by the application of various modes of treatment are presented in Table 32. The total number of determinant cases (cf. p. 20) is 575, and of these 303, or 53 per cent, have been symptomless for five years after the termination of primary therapy.

TABLE 32.
Five-year results in 638 cases of laryngeal cancer according to treatment

Treatment	Total number of cases	Number of determinant cases	Symptomless after 5 years Cases	Per cent	Recurrence within 5 years Cases	Per cent
Thyrotomy and tumor excision	33	33	22	67	11	33
Supraglottic laryngectomy	6	6	3		3	
Total laryngectomy	47	44	19	43	25	57
Total, surgery alone	*(85)*	*(83)*	*(44)*	*(53)*	*(39)*	*(47)*
Thyrotomy and tumor excision + X-ray	50	47	32	68	15	32
Supraglottic laryngectomy + X-ray	16	15	9		6	
Supraglottic laryngectomy + lymph node extirpation + X-ray	7	7	4		3	
Supraglottic laryngectomy + radical neck dissection + X-ray	11	10	5			
Total laryngectomy + X-ray	83	77	42	55	35	45
Total laryngectomy + lymph node extirpation + X-ray	40	39	15	39	24	61
Total laryngectomy + radical neck dissection + X-ray	12	12	3		9	
Total, surgery + X-ray	*(225)*	*(207)*	*(110)*	*(53)*	*(97)*	*(47)*
Total, X-ray alone	*(325)*	*(285)*	*(149)*	*(5)*	*(136)*	*(48)*
Total	638	575	303	53	272	47

Considering the total material as a single whole, practically the same end results have been achieved by surgery alone combined surgery and X ray therapy and X ray therapy alone (53, 55, and 52 per cent) (Table 52)

The five-year-cure rates in the treatment of *Stage I supraglottic* and *glottic* tumors are presented in Table 53.

The X ray treatment of *Stage I supraglottic* tumors yielded a cure rate of 73 per cent (24/33) (Table 53) Six patients out of ten survived after surgical treatment (6/10). On account of the small number of patients undergoing surgery there could be no reliable comparison of the results of treatment.

In the treatment of *Stage I glottic* tumors, the cure rates achieved with surgery and with X ray therapy alone were approximately the same (96 per cent and 93 per cent) (Table 53) Postoperative irradiation was not observed to improve the results.

TABLE 53.

Five-year results in 45 supraglottic and 89 glottic cases of laryngeal cancer in Stage I according to treatment

Treatment	Total number of cases	Number of determinant cases	Symptomless after 5 years Cases	Per cent	Recurrence within 5 years Cases	Per cent
			Supraglottic			
Supraglottic laryngectomy	2	2	1		1	
Total surgery alone	*( )*	*(2)*	*(1)*		*(1)*	
Thyrotomy and tumor excision + X-ray	2	2	1		1	
Supraglottic laryngectomy + X-ray	5	5	3		2	
Total laryngectomy + X-ray	1	1	1		—	
Total, surgery + X-ray	*(8)*	*(8)*	*(5)*		*(3)*	
Total X-ray alone	*(35)*	*(33)*	*(24)*	*(73)*	*(9)*	*(27)*
Total	45	43	30	70	13	30
			Glottic			
Thyrotomy and tumor excision	13	13	1		—	
Thyrotomy and tumor excision + X-ray	11	10	9		1	
X-ray alone	63	57	53	93	4	7
Total	89	80	75	94	5	6

Comparing the results achieved by X ray alone in the treatment of *Stage I supraglottic* and *glottic* tumors, it will be noted that the salvage rate of 73 per cent for the supraglottic group is poorer than th rate of 9› per cent for the glottic group (P < 0 01)

The five-year-cure rates for cases of *supraglottic* and *glottic* tumors in Stage II are presented in Table ›4

TABLE 34

Five-year results in 10 supraglotti and 98 glotti cases f laryng al can er in Stage II according to treatment

Treatment	Total number cases	Number determinant cases	Symptomless fter 5 years Cases	Per cent	Recurrence within 5 y rs Cases	Per cent
			Supraglottic			
Thyrotomy and tumor excision	5	5	2		1	
Supraglottic laryngectomy	1	1	–		1	
Total laryngectomy	26	25	11		14	
Total surgery alone	*(30)*	*(29)*	*(13)*	*(45)*	*(16)*	*(55)*
Thyrotomy and tumor excision + X-ray	8	5	4		1	
Supraglottic laryngectomy + X-ray	8	7	6		1	
Total laryngectomy + X-ray	44	41	22		19	
Total, surgery + X-ray	*(60)*	*(53)*	*(32)*	*(60)*	*(21)*	*(40)*
Total, X-ray alone	*(120)*	*(106)*	*(41)*	*(39)*	*(65)*	*(61)*
Total	210	188	86	46	102	54
			Glottic			
Thyrotomy and tumor excision	16	14	6		8	
Total laryngectomy	9	8	3		5	
Total, surgery alone	*(25)*	*(22)*	*(9)*	*(41)*	*(13)*	*(59)*
Thyrotomy and tumor excision + X-ray	21	17	11		6	
Total laryngectomy + X-ray	12	12	5		7	
Total, surgery + X-ray	*(33)*	*(29)*	*(16)*	*(55)*	*(13)*	*(45)*
Total, X-ray alone	*(40)*	*(31)*	*(20)*	*(65)*	*(11)*	*(35)*
Total	98	82	45	55	37	45

The five-year cure rate in the *Stage III supraglottic* group is 47 per cent (45/98), or practically the same as that scored for the Stage II supraglottic group (46 per cent, 86/188) (Tables 34 and 35)

Eight patients of fourteen were cured treatment by surgery alone (8/14) and five of 27 by X ray therapy alone (5/27) Combined surgery and X ray cured 32 cases of 57 (56 per cent) The most frequently performed operation in this group was total laryngectomy (59 determinant cases)

The result obtained with X ray therapy alone in this group is poorer than the result obtained with surgery alone or with combined treatment ($P < 0.01$)

Of the cases in the $T_1N_1M_0$ group of *supraglottic* tumors, eight of twelve survived. The most generally utilized mode of treating the primary lesion was supraglottic laryngectomy to which nine patients were subjected, seven of them receiving post operative radiotherapy as well. The end result was 5/9

The result obtained treating the $T_2N_1M_0$ group was 20/39 Three of five patients survived treatment by surgery alone, and two of nine by X ray therapy alone. Combined surgery and irradiation gave figures of 15/25 As for the surgical procedures, thyrotomy was used in three cases (result 2/5) supraglottic laryngectomy in four (result 4/5) and total laryngectomy in seventeen (result 9/17)

Of the *supraglottic* cases in the $T_3N_1M_0$ group three of six patients were cured by surgery alone and two of seventeen by X ray therapy alone. Combined surgery and X ray therapy resulted in the survival of 12 patients out of the 21 treated.

In the *Stage III supraglottic* group lymph nodes suspected of being metastatic were removed from the necks of 33 patients in conjunction with the primary operation (33/98) In ten cases a radical neck dissection was performed, and in 25 cases individual lymph nodes were removed from the neck. In all 33 cases postoperative X ray therapy was also given. In fourteen cases the excised lymph nodes were found under histological examination to be metastatic, while in the remaining 19 cases no cancer tissue was detected. Five cases in the former group remained symptomless for over five years (5/14) and thirteen cases in the latter group (13/19)

In the *glottic* group there were 17 determinant *Stage III* cases, of which seven were cured (Table 35)

Separate lymph nodes were excised from the necks of three patients with *Stage III glottic* cancer in conjunction with primary surgery In all these cases the lymph nodes were found to be metastatic. Not one of the patients remained alive after five years (0/3)

In the *Stage III* cases, no statistically significant difference between the results of treatment given in the *supraglottic* and *glottic* groups can be observed.

Table 36 presents the cure rates achieved in the treatment of *supraglottic* tumors of Stage II

The cure rate for *Stage II supraglottic* tumors is 21 per cent, or 14/66 (Table 36) Not one patient in the group was cured by surgical treatment alone (0/3) X ray therapy alone cured two patients of 23 so treated (9 per cent) Twelve of 40 patients survived after being treated by combined surgery and X ray (30 per cent) X ray therapy alone was given the four cases who upon admission were found to have distant metastases in the lungs. None of them survived

No statistically significant differences were noted in this group between the results obtained by the different modes of treatment.

The material included one case of a *Stage II glottic* tumor. The patient was a 46-year-old man whose primary lesion was situated in the right vocal cord, from which it had spread to the right ventricular band, the subglottis and the trachea (T). On the right side of the neck there were small, palpable mobile lymph nodes (N). As to histological structure, the tumor was poorly differentiated. The patient was subjected to total laryngectomy and given postoperative X-ray therapy. For two years the patient was given follow up check ups and found symptomless, but he died three years after the operation. The cause of death is not known.

TABLE 36.
Five-year results in 72 supraglottic cases of laryngeal cancer in Stage II according to treatment

Treatment	Total number of cases	Number of determinant cases	Symptomless after 5 years		Recurrence within 5 years	
			Cases	Per cent	Cases	Per cent
Supraglottic laryngectomy	1	1	–		1	
Total laryngectomy	3	2	–		2	
Total, surgery alone	*(4)*	*(3)*	–		*(3)*	
Thyrotomy and tumor excision + X-ray	1	1	–		1	
Supraglottic laryngectomy + X-ray	2	2	–		2	
Supraglottic laryngectomy + lymph node extirpation + X-ray	1	1	–		1	
Supraglottic laryngectomy + radical neck dissection + X-ray	6	5	2		5	
Total laryngectomy + X-ray		5	3		2	
Total laryngectomy + lymph node extirpation + X-ray	20	19	6		13	
Total laryngectomy + radical neck dissection + X-ray	7	7	1		[illegible]	
Total, surgery + X-ray	*(42)*	*(40)*	*(12)*	*(30)*	*(28)*	*(70)*
Total, X-ray alone	*(26)*	*(23)*	*(2)*	*(9)*	*(21)*	*(91)*
Total	72	[illegible]	14	21	[illegible]	[illegible]

DISCUSSION

Upon examining the end results for the whole material as one group (Table 32) we noted that surgical treatment alone, combined surgery and X ray therapy and X ray therapy alone had yielded approximately the same five-year-cure rates (55 55 and 52 per cent, respectively)

The conclusion cannot be drawn on this basis, however that it is all the same what method is used in treating cancer of the larynx. All three aforementioned modes of treatment were used in highly different cases and the radicalness of the operations varied considerably The efficacy of the various modes of treatment and surgical procedures can be adequately judged only after the material has been classified and equivalent groups formed on the basis of the site and extent of the tumors and other similar factors.

The classification of the material at hand according to stage criteria and the T.N.M. system has in a fundamental way facilitated the making of comparisons between the results obtained with different modes of treatment.

In *Stage I cases* good results were achieved by X ray therapy alone in both the supraglottic and glottic groups (73 per cent and 93 per cent)

Only 10 cases in the material classified as *Stage I supraglottic* tumors were treated by surgery (salvage rate 60 per cent) and the small number of these cases precludes reliable comparison with the results obtained in other groups. According to *Ogura* (1958) treatment by supraglottic laryngectomy has given quite as good results in such cases as has radiotherapy alone. *Leroux Robert* (1956) and *Letcher* (1961) believe that postoperative radiotherapy should also be given

In the treatment of *Stage I glottic* tumors, the cure rates achieved with thyrotomy (laryngofissure) and radiotherapy alone are equally good (*Leroux Robert* 1956, *Ogura* 1962, *Bryce* et al. 1963) The administration of postoperati e irradiation in these cases s not deemed imperative, for it has not been observed to have any salutary effect on results excellent in themselves (*Leroux Robert* 1956 *Ogura* 1962)

The results achieved in the treatment of *Stage I* carcinomas of the *vocal cords* included in the present material correspond to those reported in the literature, and the cure rates were equally good whether surgery or X ray therapy alone was used (96 and 93 per cent) Of late years, the Otolaryngological Hospital of the University of Helsinki has favored radiotherapy alone in the treatment of these tumors. The reason for selecting this method of treatment is that the functioning of the larynx is preserved better by irradiation than surgery This was the conclusion reached also by *Ruka* and *Lauerma* (1967) in their phoniatric follow up in estigation of patients treated by X ray therapy and by surgery

The results obtained by d fferent methods aried considerably in the treatment of *Stage II* tumors In the supraglottic group the best surv val rate (60 per cent) was achieved by combined surgery and X ray therapy No difference between the results achieved by these method of treatment could be noted in those cases in which the tumor was still situated in the supraglottic region ($T_2N_0M_0$) The clear superiority of the combined procedure in comparison w th surgery alone or X ray therapy alone was evidenced in the T_1N_1M and $T N M_0$ groups

In the *Stage II supraglottic* cases included in the material t tal laryngectomy and postoperative radiotherapy gave a 54 per cent rate of cure Th corresponding result in *Leroux Robert's* (1959) series was 61 per cent (50/82)

In corresponding cases, *Pietrantoni* and *Fior* (1958) obtained a result of 48 4 per cent by total laryngectomy alone (16/35) The figure rose to 65 1 – 69 8 per cent when the authors added to the operation a unilateral or bilateral radical neck dissection. It i possible that a better result could have been achieved also in the cases ncluded in the material at hand had radical neck dissection been used as an dditional measure toward preventing metastases of the lymph nodes.

The total result (55 per cent) obtained in the treatment of *Stage II* carcinoma f the *vocal cords* is so much inferior to the corresponding figure *for Stage I cases* (94 per cent) that it has given cause for in estigating the possibility f errors in the determination of indications for the treatment of certain types of tumors.

When the motility of the vocal cords was normal, good results could be obtained by X-ray therapy alone The rate of cure was further improved by the fact that both cases of recurrence were salvaged by subsequent measures. *Hesse* and *Baylis* (1966) have recommended that such cases be included in the Stage I class.

Fixation in the vocal cords, even when the lesion has not extended beyond the vocal cords, has caused a pronounced worsening in the cure rate in the present material, too as compared with the preceding group The right procedure for such cases is not radiotherapy alone but total laryngectomy and postoperative radiotherapy (*Pietrantoni* and *Fior* 1958, *Kleinsasser* 1961 c, *Ogura* 1962)

The combined course of treatment yielded a 61 per cent cure rate in the cases where the lesion had spread beyond th glottic region. The results obtained by surgical treatment alone were extremely poor (27 per cent) It is noteworthy that X-ray therapy alone resulted in a survival rat of 78 per cent (11/14) In these cases, the tumor had, to be sure, extended beyond the region of the vocal cords the motility of which, however, remained normal.

In the light of the foregoing, it may be stated that the fixation f the vocal cords, signifies a far poorer prognosis when treated by for example irradiation than the superficial extension of the tumor beyond the region of the vocal cords.

In the treatment of *Stage III supraglottic* tumors, principal attention was given to the primary lesion. Radical neck dissection was resorted to in nly ten cases. The results of treatment proved to be fairly good (57 per cent, 32/57) particularly by a combination of surgery and X ray therapy

Only 19 per cent (5/27) of the *Stage III supraglotti* cases were cured by radiotherapy alone.

The results as a whole obtained in the treatment of *Stage III* carcinomas of the *vocal cords* (41 per cent) correspond by and large to th survival rate for supraglottic carcinoma (47 per cent). In these cases, it i th existence of metastati lymph nodes that determines the prognosis in the main, the site of the prim ry tumor being of less significance. Toward the improvement of the results, radical neck dissection is equally indicated in both supraglottic and glottic cases.

The prognosis for *Stage II supraglottic* tumors is very poor on account of the spread of the lesion, the fixation of metastatic lymph nodes and, in a few cases, also the occurrence of distant metastases.

By means of combined surgery and radiotherapy it has nevertheless been possible to salvage 30 per cent (12/40) of these cases. X ray therapy alone must be considered mainly a palliative measure in cases where the tumor could no longer be treated surgically. However it cannot be dismissed as ineffective for two patients of 23, or 9 per cent, were successfully cured by irradiation

IX FAILURE OF TREATMENT

A Survey of literature

The recurrence of cancer in the larynx can develop in several d ff rent ways. A recurrence may develop locally either alone or in conj nction with metastases of cervical lymph nodes. In many instances, the patient may be symptomless as far as the primary lesion is concerned but the disease may recur in the form f cerv cal metastases. The recurrence of the disease may take pl ce further in the form of distant metastases, either alone or in conjunction with a local recurrence and/or cervical metastases.

A local recurrence generally develops during the first couple of years after surgical or radiation treatment (*Harris* et al 1954 *Norris* 1959) According to *H fer* and *Kroath* (1956) 88 per cent of local recurrences develop during the first year following the termination of treatment.

A local recurrence can develop from undestroyed malignant cells or such cells remaining in the marginal area from some precancerous marginal layer or from small lymph node metastases not removed during the operation or not destroyed b irradiation (*Leicher* 1963 b) According to *Leicher* (1963 b), it is frequently difficult to know whether a local recurrence or a metastasis is in question. The most frequent cause of a recurrence however is believed to be undestroyed or unremoved met static lymph nodes (*Pietrantoni* and *Fior* 1958, *Suter* 1960). The development of a recurrence in the tracheal stoma is attributed to metastases occurring in the pre- and paratracheal lymph nodes rather than to any local recurrence proper (*Ogura* 1955 *Ormerod* and *Shaw* 1956, *Suter* 1960) On the other hand, *Mårtensson* (1967) has pointed out that 50 per cent f the subglottic extensions f carcinomas of the vocal cords remain unnoticed when the diagnosis is m de and that a recurrence developing, for example after a course of radiotherapy is due most frequently to subglottic extension not d tected during the primary stage. This researcher s finding was that in cases of glottic carcinoma with subglottic extension the prognosis is very poor both after surgery and irradiation

Pathologic-anatomic investigations into the network of laryngeal lymphatics and the cervical lymph vessels and lymph nodes have provided the substance for the information we have at our disposal in studying the spread f laryngeal cancer in the cervical lymph nodes.

According to th studies of *Rouviere* (cited in *Pietrantoni* and *Fior* 1958) the larynx contains two separate networks of lymphatic ducts: the supraglottic nd the subglottic. The boundary between them consists of the vocal cords, in which lymph vessels are extremely sparsely situated. It is for this reason that supraglottic tumors practically never spread below the level f the vocal cords and vice versa The lymph vessels f the larynx have no anastomoses, as in other parts of the body into the venous ci

culatory system. The metastases do not, for this reason, always occur — depending on the location of the primary lesion — in the same lymph node. In some instances, all the lymph nodes may become affected at the same time.

The cervical lymph nodes further serve as effective filters against the advance of cancerous cells. This explains the fact that even when a patient might have cervical metastases, he can be cured of the disease by radical neck dissection, including the extirpation of the lymph nodes and vessels in which the malignant cells have been caught (*Pietrantoni* and *Fior* 1958)

Terracol and *Bringer* (1948) observed in their studies of the laryngeal lympatic network that very few lymph vessels extend from the vocal cords into the neck. No connections have been observed between the lymph vessels of the vocal cords and the supraglottic region. In the midportions of the laryngeal surface of the epiglottis, a sparse occurrence of lymph vessels could be found. There is an abundance of lymph vessels in the aryepiglottic fold and in the interarytenoid region and the network is denser in the posterior parts of the larynx.

The lymph vessels of the supraglottic area run on both sides of the neck into the lymph nodes situated in the region of the cervical blood vessels (the upper deep cervical glands). The lymph vessels of the vocal cords and the subglottic region proceed at first into the prelaryngeal lymph node from which the lymph vessels proceed in part into the deeper lymph nodes (lower deep cervical glands) situated in the lower parts of the neck and in part into the pre- and paratracheal lymph nodes (*Terracol* and *Bringer* 1948)

Pietrantoni and *Fior* (1958) *Pietrantoni* et al. (1962) have together with many other researchers, come to the conclusion that the metastasization of laryngeal cancer into the neck is mainly dependent on the location of the tumor in the larynx.

In the material published by *Leicher* et al (1956) it was observed that carcinomas of the vocal cords metastasized into the cervical lymph nodes very seldom (0.8 per cent) whereas supraglottic tumors metastasized much more frequently (25—65 per cent depending on the location of the tumor in the supraglottic region) Similar results have been reported by among others, *Ogura* and *Bello* (1952) *Pietrantoni* (19 5) and *Kuhn* et al. (1957)

A cervical metastasis is on occasion likely to be the first sign of the existence of cancer (*Pietrantoni* and *Fior* 1958, *Leicher* 1963 b)

Jackson and *Norris* (1961) stated that after total laryngectomy with or without neck dissection clinical recurrence of disease develops postoperatively as a metastasis twice as frequently as in the form of a local lesion. *Pietrantoni* et al. (1962) also consider the chief cause of failure in surgical treatment the secondary metastasization of the tumor into the cervical lymph nodes whether separately or in conjunction with a local recurrence

Hematogenic spread of laryngeal cancer is considered to be rather rare In many statistical reports, distant metastases account for only between one and four per cent of the cases (*Ducuing* and *Calvet* 1948, *Fabbi* 1952, *Pietrantoni* and *Fior* 1958) *Gowen* and *de Suto-Nagy* (1963) found that in cases of carcinoma involving the head and neck, the occurrence of distant metastases is far more frequent than the foregoing figures (56 per cent)

Distant metastases have been traced more frequently to tumors situated in the supraglottic than in the glottic or subglottic regions (*Terracol* and *Bringer* 1948, *Pietrantoni* and *Fior* 1958, *Zechner* and *Lauerma* 1967)

Usually distant metastases are situated in the lungs In the study publ shed b *Pietrantoni* and *Fior* (1958) in 14 out of 24 cases the distant lesions were in the l ngs while *Gowen* and *de Suto-Nagy* (1963) found 8? per cent of the distant met stases in their material to be situated in the lungs.

Distant metastases sometimes exist upon the patient's admission t hosp tal *Lecher* (1965 b) emphasizes, in view of this possibility the necessity of X ra examinations for every new case of laryngeal cancer The lungs should be ex mined in every case and, according to whatever symptom might ppear other p rts of th body a well.

B Failures at different clinical stages in the present material

1 GENERAL

Among the 575 determinant cases in the m terial t h nd, the prim ry treatment was found t ha been unsuccessful in 2?? cases (47 per cent) on accou t of recurrence of the cancer before the end of the five-year observation period or of operati com plications. A summary f the causes of failure is presented in Table 57

TABLE 57

Cause of failure in ?72 supraglottic and glottic cases f laryngeal cancer

Cause f f ilure	T tal umber f recurrent cases: Cases	Per cent	Supraglottic: Cases	Per cent	Glottic: Cases	Per cent
Local recurrence	61	22	40	18	21	40
Local recurrence + cervical metastases	69	25	62	28	7	13
Cervical metastases	66	24	53	24	13	23
Distant metastases	65	24	56	25	9	1
Operati and postoperati death	11	5	9	5	2	5
Total	272	100	220	100	52	100

The frequency of occurrence in the material of local recurrences and cervical metastases was practically the same (47 and 49 per cent). Twenty four per cent of the patients died of clinically and/or roentgenologically discovered distant metastases. Five patients died on the operating table and six within five weeks after the operation.

The causes of failure are presented in further detail in Tables 38, 39, 40, and 41.

TABLE 38.
Cause of failure in 220 supraglottic cases of laryngeal cancer according to clinical stage

Stage	Number of determinant cases	Number of recurrent cases	Site of recurrence				Operative death
			Local recurrence	Local recurrence + cervical metastases	Cervical metastases	Distant metastases	
I	43	15	4	1	5	5	—
II	188	102	[illegible]	15	21	30	6
III	98	55	6	24	15	6	2
IV	66	[illegible]	—	22	14	15	1
Total	39	220	40	62	55	56	9

TABLE 39
Cause of failure in [illegible] glottic cases of laryngeal cancer according to clinical stage

Stage	Number of determinant cases	Number of recurrent cases	Site of recurrence				Operative death
			Local recurrence	Local recurrence + cervical metastases	Cervical metastases	Distant metastases	
I	80	5	5	—	—	2	—
II	82	37	14	4	11	6	2
III	17	10	4	3	2	1	—
IV	—	—	—	—	—	—	—
Total	179	52	21	7	15	9	2

TABLE 40
Cause of failure in [illegible]20 supraglottic cases of laryngeal cancer according to the primary treatment

Treatment	Number of determinant cases	Number of recurrent cases	Site of recurrence				Operative death
			Local recurrence	Local recurrence + cervical metastases	Cervical metastases	Distant metastases	
Surgery alone	[illegible]	[illegible]	4	6	4	3	9
Surgery + X	1	—		23	[illegible]	20	—
X radiation	[illegible]	117	20	31	[illegible]	33	—
Total	[illegible]	220	40	[illegible]	55	56	9

TABLE 41

Cause of failure in 52 glottic cases of laryngeal cancer according to the primary treatment

Treatment	Number of determinant cases	Number of recurrent cases	Site of recurrence: Local recurrence	Local recurrence + cervical metastases	Cervical metastases	Distant metastases	Operative death
Surgery alone	35	13	4	1	6	–	2
Surgery + X-ray	49	20	5	1	7	7	–
X-ray alone	95	19	12	5	–	2	–
Total	179	52	21	7	13	9	2

2. LOCAL RECURRENCE

Of the cases of recurrence in the *supraglottic* group, 18 per cent were strictly local, while in the glottic group, the corresponding figure was 40 per cent (Table 37).

A local recurrence alone developed most frequently in Stage II carcinoma cases (supraglottic 30/40 and glottic 14/21) (Tables 38 and 39).

In the *supraglottic* group, a local recurrence developed most frequently (29/40) after X-ray therapy alone (Table 40). In the *glottic* group, a local recurrence developed after radiotherapy alone in twelve cases (12/21) (Table 41). After a thyrotomy a local recurrence developed in five cases belonging to the glottic group. In two of these cases, the primary lesion of the $T_2N_0M_0$ group had caused a fixation of the vocal cord on the side of the tumor, while in the remaining three cases the primary lesion had spread to the supraglottic region ($T_3N_0M_0$).

3. LOCAL RECURRENCE AND CERVICAL METASTASES

Among the cases in which the disease recurred both locally and in the form of cervical metastases (Table 37), 62 belong to the *supraglottic* group with respect to the nature of the primary tumor and seven to the *glottic* group. Seventy-four per cent (46/62) of the patients in the supraglottic group had palpable cervical lymph nodes upon admission (Stages III and IV, Table 38).

Precisely one-half of the 62 cases in the supraglottic group had primarily received radiotherapy alone (Table 40). Of the 25 cases of recurrence following combined surgery and X-ray therapy, as many as 21 belonged to the third and fourth stages (Table 38 and 40). Eleven of these 21 had had metastatic lymph nodes removed in conjunction with the primary operation.

Seven patients in the glottic group (Table 37) developed a local recurrence together with cervical metastases. Four of them had second and third stage tumors to begin

with (Table 39) In four cases the primary lesion had been situated in the region of the vocal cords ($T_3N_0M_0$ and $T_2N_1M_0$) and the tumor had caused a fixation of the vocal cord(s) In three cases the tumor had already primarily extended beyond the region of the vocal cords ($T_3N_0M_0$ and $T_3N_1M_0$) Of these seven patients, five had received irradiation exclusively as primary treatment (Table 41).

4 CERVICAL METASTASES

In 24 per cent of the cases of recurrence (66/272) the disease recurred in the form of cervical metastases alone (Table 57) In 53 cases, the primary tumor belonged to the supraglottic group (53/66) and in 13 cases it belonged to the glottic group (13/66)

In the supraglottic group (Table 58) cervical metastases appeared in 24 cases in which palpable lymph nodes had not been detected during the primary therapy (Stages I and II) and in 29 cases in which palpable lymph nodes had been present primarily (Stages III and IV) In this group there occurred the largest number of cervical metastases without local recurrences among Stage II carcinoma cases (21/53) Of these 13 cases belonged in the $T_2N_0M_0$ group in which the tumor was still in the supraglottic region (13/21) In eight other cases (8/21), the primary lesion had extended beyond the supraglottic region, in three of these cases even beyond the confines of the larynx.

Of the 13 cases of cervical metastases in the glottic category eleven represented the second stage and two the third (Table 39) In one case the primary lesion had been confined to the glottic region but fixation had already taken place. In the remaining 12 cases, the tumor had spread beyond the region of the vocal cords ($T_3N_0M_0$) In six cases the cervical metastases had developed in this glottic group following surgical therapy exclusively (four thyrotomies and two total laryngectomies) and in six cases following combined treatment (four thyrotomies and two total laryngectomies) (Table 41)

Cervical metastases caused a recurrence of the disease in a total of 155 cases, or in 24 per cent of the 575 cases in the material as a whole. In 69 cases cervical metastases appeared in conjunction with local recurrences, and in 66 cases alone Secondary metastases occurred in 55 cases in which there had been no palpable lymph nodes upon hospital admission (55/393 or 14 per cent) and in 80 cases in which palpable lymph nodes had been present upon admission (80/181 or 44 per cent) In the latter group the frequency of secondary metastases is greater than in the former ($P < 0.001$)

In the supraglottic group a secondary cervical metastasis developed in a total of 115 cases (115/[illegible] or 20 per cent) In the cases in which no palpable lymph nodes were present on admission, secondary metastases developed in 40 cases (40/2[illegible]1 or 17 per cent) In those cases in which palpable lymph nodes were present on admission secondary metastases developed in [illegible] cases (75/164 or 46 per cent) In the latter group the frequency of occurrence of secondary metastases is highly significantly greater statistically ($P < 0.001$)

In the glottic group secondary meta tases developed in 20 cases, all told (20/179 11 per cent). Of the cases, 15 had no palpable lymph nodes on admission to hospital (15/162, or 9.5 per cent) and five did have palpable ones at the time (5/1 or 29 per cent). No statistically significant difference could be bserved between the tw last-mentioned groups.

In the group compris ng supraglottic tumors, the frequency of secondary nodal metastases (29 per cent 115/395) is greater than in the group of gl ttic tumors (11 per cent, 20/179) (P < 0.01).

5 DISTANT METASTASES

Table 57 shows that the disease recurred in 65 patients in the form f distant metastases within five years after th termi ation of treatment. Distant m tastases had been discovered in the lungs of four patients upon their admission to the hosp tal.

At the time of appearance of distant metastases, 39 patients were symptomless with regard to the primary lesion and cervical findings (39/63). Nine patients had a local recurrence in addition to the distant metastases, nine others a local recurrence and cervical metastases and eight only cervical metastases. In 56 cases (56/63 86 per cent) the primary tumor was situated in th supraglotti region, and in nine ther cases in the glottic region. There were significantly more distant metastases among the cases in the supraglottic group than among the cases in the glotti group (P < 0.01). In 43 cases the primary tumor belonged to the first and second stages (68 per cent, 43/67) and in 22 cases to th third and fourth stages (32 per cent, 22/63) (T bles 58 and 59).

Table 42 shows the sites of distant metastases.

TABLE 42.
Distribution of distant metastases in 575 determinant ases of laryngeal cancer

Site of distant metastases	Number f cases	
Lung	55	
Mediastinum	1	
Axilla	1	
Thoracic ertebrae	2	
Base of th skull	1	
Oesophagus	1	
Stomach	1	
Pylorus	1	
Urinary bladder	1	
Genitals	1	
Total	65	65/575 = 11 per cent

Overwhelmingly the greatest number of distant metastases were situated in the lungs (55/65 or 85 per cent)

The primary lesion in cases of distant metastases had been treated by X-ray therapy alone in 35 cases (54 per cent, 35/65) by combined surgery and X ray therapy in 27 cases (42 per cent, 27/65) and by surgery alone in three cases (4 per cent, 3/65) (Tables 40 and 41)

C Discussion on failures

Among the cases in the material at hand, the disease was found to reappear within five years after the termination of treatment with equal frequency in the form of a local recurrence as in that of cervical metastases. In the literature, however the recurrence of the disease is considered to take the form of cervical metastases more commonly This is true particularly of cases treated exclusively by surgery (*Jackson* and *Norris* 1961 *Pietrantoni* et al. 1967)

Obviously the chief reason for the relative frequency of local recurrences in the present material has been overoptimism in the application of non-radical methods of treatment, notably X ray therapy In *Stage I* cases, however the radicalness of treatment of the primary lesion must be deemed nearly sufficient. The results of such therapy were 87 per cent (105/125) In addition, secondary treatment resulted in the cure of three of nine cases of local recurrence.

In *Stage II* cases, local recurrence was observed to be the most common cause of reappearance of the disease in both the supraglottic and glottic groups.

In the treatment of *Stage II supraglottic* tumors, especially in T_3 cases, primary irradiation must be judged an insufficient measure in the light of the poor results obtained. In the T_3 group the lesion occurs over an extensive area primarily and if a recurrence develops, the tumor will have spread beyond the larynx. Consequently [illegible] measures have only seldom succeeded in salvaging patients belonging to [illegible] 19) In most cases, the disease has proved inoperable at the recurrence [illegible]

In the treatment of *Stage II glottic* tumors a local recurrence was observed to have developed most frequently in T_2 cases, both after surgery and after primary X ray therapy Local recurrences were most common in cases where the primary carcinoma had impaired the motility of the vocal cords or caused a fixation there

In certain Stage II cases involving the vocal cords (4/11) a local recurrence was successfully treated by later measures, notably total laryngectomy

In the *supraglottic* group local recurrences alone were observed to develop relatively less frequently than in the *glottic group*. One reason for this is that a local recurrence takes place in the supraglottic group more often in conjunction with cervical metastases than by itself

Local recurr[illegible] found [illegible] develop more frequently in conjunction with cervical meta stases [illegible] where palpable [illegible] nodes had been present in the neck already at the pr[illegible] (St[illegible] III and IV) The primary treatment had in many

instances been as radical as possible, but in advanced cases it had The majority of the cases of recurrence in this group dev lopel aft therapy alone.

Recurrences developed in the form of cervical metastaw s I (r supraglottic carcinoma. Of these cases nearly one-half w re l w metastases could not be palpated at the time of the patient dm u the hosp tal and the primary tumor most often was classif ed as belong g t St ge II In more than one-half of the cases, there were palp ble lymph nodes n the ne k on dm ssion In the former group (Stages I and II) no measures had been t k t prevent cervical metastases in conjunction with the primary therapy Only four of 3 cases could be salvaged by secondary therapy

In the latter group (Stages III and IV) meta tases l d been remo ed from t e ne k in connection with the primary treatment and radic therapy had been gi en to the neck. The results proved poor on the whole. Curative me ures in th treatment of cervic l metastases nearly always yield poor results, whether th metastases be tre ted b radical neck dissection or by irradiation (*Kleinsasser* 1961 c).

Secondary metastases developed in 29 pe cent of the supraglottic and n 11 per cent of the glottic cases included in the material at hand. *Norris* (1959) repo rt that in his material second ry metastases occurred in 30 per cent (29/ 3) of the cases in the supraglottic group In eight per cent (4/52) of those n the glottic grou n nd in 1 per cent of those in the subglottic group (9/50) W th respect to the supraglottic group in the present material, it will be noted that it includes 10 per cent fewer secondary metastases than does the corresponding gro p in *Norris* series. The difference between the glottic groups is slight. N conclusions can be drawn on the basi f the subgl ttic group in the present material because it contains only a single case

Secondary metastasization wa more frequent occurrence in the supraglottic th n in the glottic group. Metastases occurred in 17 per cent f the cases in which no pal pable lymph nodes had been present on admission and in 40 per cent of the ases in which palpable lymph nodes had been noted. In *O Keef* (1950) studies the corresponding percentages were 12.5 (5/40) and 57 5 (21 30) In the material t hand the metastases figures are somewhat higher than those reported by *O'Keefe* The difference probably is mainly due to the fact that in *O'Keef* s material radic l neck dissection was employed both a an electi e and as curati e measure which evidently resulted in cutting down the frequency of secondary metast ses It would be presumed that, in the cases covered by the present study metastases might h ccurred even more frequently particularly in the supraglotti group, inasmuch as radic l neck dissection was seldom perf rmed. However it is pparent that postoperati e X ra therapy has reduced the frequency f occurrence of metastases

Ogura (1955) contended that "the incidence f metast ses d d not ppea to be related to the size of the primary lesion, but rather to the l cation. Among Stage I cases in the present material, secondary metastases were observed, though, to onl rather small extent (4 cases)

Distant met stases occur in the material n relat bundance (11 per cent, n 37%). In general, l ry geal cancer is regarded as disease that seldom spawns d sta t metastases (e.g., 4 per cent f the cases in *Pietrantoni* nd F (1958) in ten l)

II and one Stage III Of the cases in the glottic group one belonged to Stage I and four to Stage II.

Therapeutic measures were taken in 40 cases of local recurrence and simultaneous cervical metastases, but *not one of the patients lived for five years after the secondary treatment.* The most commonly used method of treatment in these cases (23/40) was X ray therapy alone (Table 43)

Therapeutic measures were taken in 47 cases of cervical metastases alone. Four of the patients underwent radical neck dissection and were given X ray therapy besides. One of the four remained symptomless five years after the dissection (1/4) In sixteen cases isolated metastatic lesions were removed from the neck and X ray treatment was then given. Two of these cases remained symptomless five years after the treatment (2/16). In 27 cases X ray therapy was used in cervical metastases, and one of the patients was symptomless five years after treatment (1/27)

DISCUSSION

Taken as a whole little has been achieved in the treatment of recurrences. Sixteen cases could be cured by later measures (16/272) twelve of them being a local recurrence. *Meinsasser* (1961 c) considers total laryngectomy to be the only method of successfully treating a local recurrence He looks upon radiological therapy for example, as contraindicated in these cases. Total laryngectomy has been observed also in the material at hand to produce the most favorable results in the treatment of local recurrences.

The treatment of cervical metastases at the recurrence phase gave poor results (4/156) According to *Clerf* (1955) for example a cure rate of between 10 and 35 per cent can be obtained in the treatment of secondary metastases by radical neck dissection. In the cases contained in the present material, dissection was used ten times in the treatment of secondary metast ses, and one of the pati nts survi ed

E Operative and postoperative mortality

During the early period of surgical treatment of laryngeal cancer in the last century operative mortality wa nearly 50 per cent, wherea nowadays it is only a few per cent. The chief reason for this development i the improvement in surgical procedures and later on the use of antibiotics and the development of nesthetic methods.

The head ng of operative mortal ty also embraces the cases that ended in death with n four or five weeks after surgery In *Leroux Robert s* (1961) material, the operative mortality was 4 per cent, and in *Pietrantoni and Fior i* (19 8) 2.7 per cent.

According to *Ogura* and *Bello* (19) and *Pietrantoni* and *Fior* (19 9) neck dissection has not been observed to increase the perati leatl rate

Operations were performed on 313 patients in the present material (313/638) Five of the patients died on the operating table (1.6 per cent, 5/313) three of them from heart complications and two from hemorrhage Six patients died within five weeks after the operation (1.9 per cent, 6/313) Two of them died of heart complications, one of a hemorrhage caused by the feeding tube (from an anomalous arteria subclavi) two of pneumonia and one of uremia. The total operati e and post perative death rate amounts to 3.5 per cent of the material (11/313)

The average age of the aforementioned 11 patients was 61 years. The youngest patient in this group was 50 years old and the two ldest were 72.

DISCUSSION

The operative and postoperative death rate of 3.5 per cent registered in the present study corresponds by and large to the figures cited in the literature. (For example those published by *Pietrantoni* and *Fior* (1958) 13/570, 2.3 per cent)

Radical neck dissection has not increased the perati e mortality in the present material. The number of such operations is, t be sure small — only 24 cases.

X GENERAL DISCUSSION AND CONCLUSIONS

Present-day research into the methods of treating laryngeal cancer is mainly based upon the same trial-and-error approach and statistical comparison of the results of treatment as were used during the last century. Research reveals great progress. For example, operative mortality has been reduced to a fraction of what it was during the early period of surgical treatment of laryngeal cancer. This has been achieved in spite of the fact that the patients are apt to be in weak condition and elderly and the surgical procedure, furthermore, exceedingly radical. On practically equal terms with surgery, progress has similarly been made in the methods of treating cancer of the larynx by irradiation. Contemporary methods insure the survival of approximately every second laryngeal cancer patient.

As research makes advances and the methods of treatment develop, efforts are made to achieve ever greater accuracy in the determination of therapeutic indications, principally on the basis of the site, extent and, in part, also the histology of the tumor. The consequence of this is, however, that even large series are apt to be divided into *such small categories that the results obtained can no longer be statistically compared* in any significant way. In other words, the more detailed and exact the classification of different types of cases — which evidently further have varying prognoses — the poorer becomes the statistical reliability, unless the number of comparable cases correspondingly increases. In at all rare cases, the data compiled in a single hospital or even a single country do not suffice to make a statistically reliable comparison between the results obtained by different methods of treatment, because the number of cases is simply too small. Similar cases are likely to be treated in different hospitals over a period of a few years and the results of treatment are published in sufficient quantity to insure a highly reliable statistico-mathematical comparison, but on account of the differences between the methods of classifying the material, there is no adequate guarantee of their mutual correspondence.

With the arrangement of therapeutic indications being based, according to the TNM system and clinical staging, on far more detailed and exact determination of the site and extent of the tumor than earlier, the necessity for the individual physician and hospital to draw mainly on their own experiences are reduced. The scattering of the facilities for the treatment of laryngeal cancer cases all over Finland through recent changes in the organization of the national hospital system represents in certain respects a retrogressive development from the standpoint of effective study and possibly therapy as well. On the other hand, the necessity of depending more than ever on the broad experience gained in the international field could, on the strength of far more accurate and reliable data, compensate for this negative trend, as could *also the opportunities opened up to admit patients, perhaps, to treatment at an earlier* stage than before.

The results of treatment of laryngeal cancer depend, according to the current view, mainly on the site and extent of the tumor, possible cervical metastases and the

existence of possible distant metastases. In addition, at least the histology f the tumor influences the prognosis. For example the present material includes 24 carcinoma in situ cases, which *without exception were cured by X ray therapy alone.*

So far it has been possible to explain the factors ffecting the location of a primary lesion only in very small measure Different national ties have their own special characteristics in this respect, being due to for instance habits of eating, using tobacco and drinking alcoholic beverages, condition of teeth, s well as to racial features, climatic conditions and ther similar circumstances

With respect to the site of the primary tumor Finland is in an exceptionally bad position. In just about all the studies concerning laryngeal cancer supraglottic tumors have been found to be far more difficult to treat than glottic tumors and in the present *material* the percentage *of supraglotti lesions (67 per cent) is higher* than the corresponding figure given in any generally cited paper published abroad.

The extent of a tumor at the time of the patient s admission to hospital evidently indicates quite accurately the general medical standards prevailing in the country in question. The earlier the stage at which tumors can be correctly diagnosed and treated, the higher must the level of the local medical establishment be judged.

This truth is most clearly revealed in the medical sector embracing glottic tumors. At an early stage these lesions cause such a conspicuous hoarseness of voice that it cannot fail to escape the notice of eithe the patient himself or the persons with whom he is in continuous contact. The promptness with which a husky oiced person turns to physician depends on the level f public enlightenment in m tters of cancer treatment, and the reporting of a patient suspected of having cancer to a specialist or to special hospital for examination generally depends on th vigilance and level of training f the general practitioner If a patient with even an early-stage glottic tumor passes th routine checks of a well-equipped otolaryngological clinic undiagnosed, it must be deemed — in this era of modern diagnostic instruments, notably the stroboscope and the laryngendoscope — the result of downright carelessness or professional error. The cure rate for glotti cancer treated t Stage I by X-ray therapy alone is so excellent (in the material at hand, 94 per cent) that conditions are already ripe for the fundamental improvement f the total results in the treatment f glottic tumors. All that is required is the intensification of cancer enlightenment, together with the elimination of the elements of friction in medical organization.

As far as supraglottic tumors are concerned, early diagnosis is a basically harder nut to crack from whatever position might be taken — public enlightenment, the general practitioner the cancer specialist. The exceptionally high percentage of supraglottic tumors among cancer cases in this country makes this question an issue of particular concern in Finland. It demands very extensi research and strenuous efforts.

Quite a special problem is posed by the p tient attitude toward the recommendation of surgical treatment. Declining radiotherapy alone when recommended is extremely rare, and not a single instance ha been marked down in the card files covering the patients included in the present material. The ttitude f a patient who has undergone or is facing surgery is the same toward postoperative or preoperative irradiation. On the other hand very large proportion of laryngeal cancer patients

shrinks away from recommended radical surgical treatment, especially total laryn gectomy The patient finds it hard to adjust himself to the idea of losing his power of speech and also tends instinctively to fear a major operation In a large laryngological hospital there are likely to be a number of recently operated laryngectomy patients at the same time, and seeing them is hardly calculated to encourage anybody to join their company Also the attending physician often has a natural aversion to reducing his patient to irreversible disability even in cases where it means saving the patient's life

Of the cases contained in the present material, a total of 58 patients refused to undergo surgery and were therefore treated by X-ray therapy Fifty of them were determinant cases, and 11 or 22 per cent, survived. If these cases, which were dealt with contrary to the opinion of the attending physician, are omitted from the group that were treated by primary X ray therapy alone the five-year-cure rate for the group would rise from 5? to 59 per cent.

The material contains a total of 315 surgical patients. All told, 371 patients were advised to accept surgical treatment, but 16 per cent, or nearly one out of every six, refused to go through with the course of treatment recommended as most suitable

A laryngeal cancer patient treated and cured by radical surgery seldom after the usual period of observation, comes into contact with the physicians who attended him Very rarely in all probability does such a physician have occasion after a lap of many years, to ask a patient his opinion of a measure that disabled him to save hi life Moreover the value of individual responses to such a question is doubtful

In this respect, considerable light is shed by a letter sent April 9 1965 to the Otolaryngological Society of Finland The letter was sent by an organization — the *LF Kerho* or LE-Club — which was founded by Finnish laryngectomy patients to support their common rehabilitation aspirations and which has a membership of over 300 The letter mainly deals with raising the statutory disability level of such patients from 50 to 80 per cent in order to improve their difficult economic situation, but it also contains a passage that reveals at lea t the majority opinion among these patients as to radical surgery We are aware of and recognize as altogether justified the plan whereby in future the operation must be sufficiently extensive to obviate the performance of new operations because of the spread of cancerous lesions beyond the original site We are also fully cognizant that many of us desired the performance of only a small operation, with the consequence of premature death or at least, continued illness The authors of the letter have the benefit of no medical training, but their observations are in the main the same as those made in the present tudy In th 575 determinant cases included in this material, the primary treatment failed in 2?2 cases, and of these only 16 patients could be salvaged by subsequent measures. There can be no question of the fact, furthermore that the authors of the letter might not be completely knowledgeable with respect to the difficulties to the patient caused by laryngectomy

A patient's acceptance of recommended radical surgery often decisi ely depends on the extent to which the attending physician has familiarized himself with the ad n tages and disadvantages of different modes of treatment in the type of case at hand and also on the extent nd way the physician expl ins matters t him. For exampl if

a patient were told only those end results of this investigation according to which a slightly better cure rate was obtained with X ray therapy alone than with combined surgery and X ray therapy he would scarcely submit to surgery not being able to comprehend that the efficacy of irradiation decisively depends on the location extent and stage of the cancer

Insofar as no fundamental improvements are mad in the methods of treatment, the chief problem will evidently be one of more precisely than up to now drawing the line past which it is necessary to abandon radiotherapy in fa or of radical surgery The solution to the problem involves both making the classification more accurate and determining the extent of each lesion with the greatest possibl precision Recently *Mårtensson* (1967) drew attention to the extension of glottic tumors to the subglottis and to the difficulties encountered in diagnosing this circumstance. W thout a transcomoscopic examination, an extension of this kind is easily apt to be overlooked with the consequence of an erroneous estimation of the extent of the tumor both in the selection of the mode of treatment and the evaluation of the results. The development of examination techniques applicable to the early di gnosis of cervical metastases would also open up new possibilities for arranging more accurat therapeutic indications than hitherto, notably from the standpoint of determining the necessity of radical neck dissection.

On the basis of the present material, the following conclusions might be drawn with respect to the therapy most appropriate to cert in types of cases.

Apparently the only group whose method of treatment can be determined solely on the basis of a histological examination is the one comprising carcinoma in situ tumors. In the present m terial there is a total of 24 such cases, and without exception they have all been cured by X-ray therapy alone.

Among supraglottic tumors, there is only one category — in addition to these carcinoma in situ cases — in which X-ray therapy alone might be recommended, namely $T_1N_0M_0$ tumors (Stage I) situated on the posterior surface of the epiglottis. The prognosis in such cases is not particularly good, either being bout 70 per cent. The surgical treatment likely to come into question in these cases is supraglottic laryngectomy There are too few cases treated by this method in the present material for the drawing of reli ble conclusions (seven patients, f whom four were cured)

In the treatment of $T\ N_0M_0$ supraglottic tumors in the Stage II group it is of great importance whether the lesion is situated near the arytenoid region or th vocal cords or not. In the former instance, a total laryngectomy would be necessary while in the latter apparently a supraglottic laryngectomy would suffice. On account of the strong tendency of supraglotti tumors to metastasize, radical neck dissection is advisable in spite f the fact th t palpable lymph nodes are not present in the cases belonging t this group. Whether the dissection should be performed on both sides or only o e side f the neck depends on the location of th tumor

In the treatment f T_3N_0M group supraglottic tumors, total l ryngectomy nd radical neck dissection are required, while in the $T_4N\ M_0$ group the treatment generally calls for laryngo-pharyngectomy and radical neck dissection. Exceptions re

such tumors of the posterior surface of the epiglottis as have not advanced beyond the base of the tongue. In these cases a supraglottic laryngectomy would suffice in lieu of a total laryngectomy.

The treatment of Stage III and Stage IV supraglottic tumors must likewise be quite radical, including, that is, total laryngectomy and bilateral radical neck dissection. In the event the lesion extends beyond the larynx, instead of a total laryngectomy a laryngo-pharyngectomy should be performed.

In Stage I cases of glottic tumors, radiotherapy alone suffices to give excellent results.

In the treatment of tumors in the glottic Stage II $T_2N_0M_0$ group the decisive circumstance is the motility of the vocal cords. If it is normal, irradiation alone suffices to give good results. If the motility of the vocal cords has been impaired or they have become fixated, it is necessary to perform either a partial resection or a total laryngectomy, depending on the nature of the case.

In the treatment of all other glottic tumors — that is, those in the $T_3N_0M_0$ and $T_4N_0M_0$ groups, as well as Stage III and Stage IV lesions — it is advisable to perform total laryngectomy and radical neck dissection.

It is difficult to draw reliable conclusions on the basis of the present material regarding the efficacy and necessity of postoperative radiotherapy in different types of cases. There are conflicting views on this matter in the literature, too. It ought to be considered mandatory at least in those cases where it is impossible to be sure of the complete eradication of the primary lesion, especially in connection with total laryngectomy. In order to prevent cervical metastases, radiotherapy must be given at least when the site of the primary lesion — e.g., the arytenoid region — indicates a great danger of metastasization and when lymph nodes removed in conjunction with a radical neck dissection are found to be metastatic.

The only truly effective treatment of recurrences is total laryngectomy and radical neck dissection in cases where these operations has not been performed in connection with the treatment of the primary lesion. Radiotherapy alone must be considered mainly a palliative measure suitable in cases where the recurrence can no longer be treated surgically.

XI SUMMARY

The material comprises 638 histologically verified cases of carcinoma and carcinoma in situ of the larynx treated at the Otolaryngological Hospital and the Radiological Hospital of the University of Helsinki during the period 1919–1959.

Of the total number of cases, 575 were found either to have lived symptomless for five or more years after the termination of treatment or to have suffered from a recurrence of the cancer. The five-year cure rates were calculated in terms of the percentage of these so-called determinant cases. The remaining 63 so-called indeterminant cases either died from causes other than cancer (35 cases) or the cause of death was unknown (22 cases) — or then they were lost to follow up (6 cases).

The average age of the patients was 55.7 years, that of the 615 males being 56.1 and of the 23 females 44.4 years. In the group consisting of supraglottic tumor cases, there was a higher percentage of patients under 51 years (37 per cent) than in the glottic group (30 per cent). The difference between these figures was found to be statistically significant.

The cases were classified on the basis of the site and extent of the tumor in accordance with the T.N.M. classification and clinical staging system. The frequency of occurrence of supraglottic tumors was found to be exceptionally high, namely 67 per cent, and that of the glottic tumors correspondingly low (33 per cent). The material contained only one subglottic tumor.

Supraglottic tumors were diagnosed at Stage I in only 10 per cent of these cases, whereas glottic tumors were diagnosed at the corresponding stage in 43 per cent of the cases. The difference between these figures was found to be statistically highly significant. With a single exception, all 75 cases diagnosed in Stage IV belonged in the class of supraglottic tumors.

In the supraglottic group 41 per cent of the cases were found to have clinically suspect cervical metastases upon the patients admission to hospital. In the glottic group the corresponding figure was 10 per cent. The difference between the percentages was found to be statistically highly significant.

The cases of the material were distributed according to their histology as follows: carcinoma in situ 4 per cent, well differentiated carcinoma 30 per cent, poorly differentiated carcinoma 47 per cent and undifferentiated carcinoma 19 per cent. Of the 24 carcinoma in situ cases, 21 belonged in the group of glottic tumors and three in that of supraglottic tumors. No significant difference between the supraglottic and glottic tumors was noted with respect to the distribution of well differentiated and poorly differentiated carcinomas but the percentage of undifferentiated growths contained in the supraglottic group (23 per cent) was highly significantly greater than in the glottic group (10 per cent).

Three main lines of treatment were followed surgical therapy alone (13.8 per cent of the cases) combined surgery and X ray (3) C per cent) and X ray therapy alone (50 6 per cent) The most frequently performed operations on the primary tumor were total larygectomy (18? cases) thyrotomy and removal of the tumor (91 cases) and supraglottic laryngectomy (10 cases) Operations on the region of the cervical lymph nodes were performed in 71 cases in all these cases, lymph nodes suspected of being meta tatic w re detected in the neck before the operation.

In the total material of 5 5 determinant cases the five-year cure rate of primary treatment f r patient between the ages of ɔ1 and 40 years (C ɔ per cent) was found to be significantly better tl an for those between 71 and 80 (1ɔ per cent) In the supra gl ttic group the prognos for patient under 51 years of age (ɔC per cent) wa highly significantly better than f r those over 51 (5ˉ per cent)

The cure rate for men (ɔ2 per cent) was below that for women (ˉ1 per cent) but th difference was not statistically gn ficant cwing to the small number of women in the material (23 cases)

All 24 carcinoma in situ cases in the material were found to be symptomless fi e years after the termination of X ray therapy In the group of carcinomas, the cure rates worsened progres iv ly a the tumors became more undifferentiated (well differentiated 61 per cent, poorly d fferent ated 48 per cent and undifferentiated 44 per cent) but no stati tically significant d fference could be found between the results obtained at the various differentiation stages.

The cure rates in the different clinical stages were as follows Stage I supraglottic tumors 70 per cent glottic 94 per cent, tot l 8ɔ per cent Stage II supraglottic 46 per cent glottic 5ɔ per cent, tot l 49 per cent Stage III upraglottic 47 per cent, glottic 41 per cent, total 46 per cent and Stage IV supraglottic cases only 21 per cent.

The most frequently applied (35/45) method of treatment in cases of Stage I supra glottic tumors was X ray therapy alone which gav a cure rate of ˉ3 per cent.

In the treatment of the 80 cases of Stage I glottic tumors, X ray therapy was used *n 57 cases,* w th a result of 93 per cent. Thyrotomy nd the removal of the t mor yielded approximately the same result (96 per cent, 22/23) as X ray therapy alone

In the treatment of Stage II supraglottic tumors, X ray therapy alone was the method most frequently used (106/185) and it gave a cure rate of ɔ0 per cent. Com bined surgery and X ray (53 cases) resulted in a cure rat of 60 per cent. Surgery alone was used to treat ?9 cases (? total laryngectomies) and th cure rate was 45 per cent. The result obtained with comb ined surgery and X ray was almost significantly better stati tically than that obtained with surgery alone or X ray therapy alone The superiority of the comb ned method did not become evident in the cases belonging to the $T_2N_0M_0$ group, n which the primary tumor was situated exclusi ely in the supra glottic region but it did become evident in th cases belonging to the $T_3N_0M_0$ and $T_4N_0M_0$ groups, in which the growth had spread beyond the region of th supraglottis.

In the treatment f Stage II glottic tumors, X-ray therapy alone resulted in a cure rate of 65 per cent (20/?1), combined surgery and X ray 55 per cent (16/29) and surgery alone 41 per ent (9/ ?) N statistically significant differences between these results could be found

The best group from the standpoint of therapy consisted of the 11 T_2N_0M cases in which th motility of the vocal cords was normal X ray therapy alone (9 cases) and thyrotomy and the removal of the tumor (2 cases) resulted in the cure primarily of 9 patients. As the two cases of recurrence were cured by subsequent measures (total laryngectomy), all eleven patients emerged as survivors.

The prognosis proved to be much poorer on the part of the 18 T_2N_0M cases the motility of whose vocal cords had become impaired or lost. Only seven of these 18 cases were cured. In the light of these results, the significance of a fixation f the vocal cords was emphasized as a bad prognostic sign and as an indication of radical treatment.

In the treatment of Stage III supraglottic tumors, the following cure rates were obtained surgery alone 57 per cent (8/14) combined su gery and X-ray 56 per cent (32/57) and X-ray therapy alone 19 per cent (5/27) The result obtained with radiotherapy alone was significantly poorer statistically than that obtained with other modes of treatment.

The Stage III supraglottic group included 33 cases in which, in conjuction with the removal of the primary lesion, either a radical neck dissection was performed (10 cases) or separate lymph nodes suspected of being metastatic were extirpated from the neck (23 cases) In the 14 cases in which lymph nodes were histologically found to be metastatic, the cure rate was 5/14 (35 per cent) and in the 19 cases in which no cancerous tissue was detected, the rate was 13/19 (68 per cent)

There were so few cases of Stage III glottic tumors (17 determinant cases) that no reliable comparison between the results obtained with various modes f treatment could be made The total cure rate in all these cases was 41 per cent (7/17)

All 66 determinant cases in Stage IV belonged to the supraglottic cancer group. Combined surgery and X-ray therapy gave a cure rate of 30 per cent (12/40) and X ray therapy alone 9 per cent (2/23) Surgery alone was used in three cases and not one of them survived for five years. In conjunction with the surgical removal of the primary lesion, 32 cases were subjected to radical neck dissection (12 cases) or had separate cervical lymph nodes extirpated (20 cases) In the remaining 34 cases, no operation was performed in th region f the cervical lymph nodes. The corresponding cure rates were 29 per cent (9/32) and 12 per cent (4/34) respectively

The primary treatment failed in 272 f th 575 determinant cases (47 per cent) The lesion reappeared in the primary site alone in 61 cases, as metastases alone in th cervical lymph nodes in 66 cases and simultaneously in both these sites in 69 cases. A total f 66 patients died of distant metastases five died on the operating tabl a d six within fi weeks fter the operation.

A local recurrence alone was most common (44/61) among the Stage II tumors, and in this regard there was no significant statistical difference between tl supraglottil (30/168) and glottic groups (14/82) A local recurrence was most common after X-ray therapy alon (41/61) while in eight cases it developed fter surgery alone and in twelv cases after combined surgery and radiotherapy

The disease reappeared in 69 cases simultaneously in the form of a lo and cervical metastases and of these cases 62 belonged to the supragl 6 per cent of these supraglottic cases (10 C2) the lymph nodes had upon the patients admission to hospital. One-half of the cases in this had received X ray therapy alone primarily. In 25 cases the treatment of combined surgery and X ray therapy and in 11 of these patients the nodes had been histologically found to be metastatic.

Lymph node metastases alone caused recurrence of the disease in 6 them involving the supraglottis. In 5 cases (5 60) no palpable lymph n present at the time of primary treatment.

All told cervical metastases caused recurrence of the disease in 1 5 metastases developed to a statistically significant extent more often ar which palpable lymph nodes had been present in the neck upon the pa sion to the hospital.

The frequency of occurrence of secondary metastases was significantly upraglottic than in the glottic group (20 and 11 per cent respectively).

Therapeutic measures were taken in 120 cases to treat a local recu cervical metastases.

Of 5 recurrences of malignancies in the primary site 12 remained sym years after the termination of secondary treatment. T t l laryngectomy produce the best results (10/18 5 per cent). Fourteen cases were treated x lu l y one of them remaining symptomless for five years.

In 40 cases a recurrence in the primary site of the disease was treated i with cervical lymph node metastases. The most frequently used method w irradiation alone (2 ses). Not one of these 40 cases were sym years after treatment of the recurrence.

Cervical metastases alone were treated in 17 cases. The most gene method of treatment was X ray therapy alone (27 ses) with which on ured. In 10 cases the metastatic lymph nodes were extirpated from th which the region operated on was irradiated two of the cases so trea symptomless for five or more years. Four patients underwent a unilateral dissection and radiation therapy and one of them remained symptom years.

All told, 10 patients with recurrence of the disease could be cured by peutic measures. The number represents 6 per cent of the cases of recurre

Sixty five patients developed clinically and/or roentgenologically ascert metastases within f years after the termination of primary treatment the primary lesion had been situated in the region of the supraglottis. A ber of distant metastases were found in the supraglottic group to a stati ficant degree than in the glottic group. Most frequently the distar occurred in the lungs (6 85 per cent). In 62 cases (62.6) the patients irradiation in conjunction with the primary therapy.

A total of 313 patients in the material underwent surgery. Five patients died on the operating table (1.6 per cent) and six others within five weeks after the operation (1.9 per cent). The entire operative and postoperative death rate in the material was 3.5 per cent.

The patient's attitude toward radical surgical treatment upon its being recommended to him was observed to constitute a special problem. The foregoing material includes 371 cases in which an operation was proposed and of which 58 patient rejected th recommendation and consequently had to be treated by radiotherapy alone.

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DIE MORPHOLOGIE DES GANGLION SPIRALE COCHLEAE

VON
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ACTA OTO-LARYNGOLOGICA NARVAVÄGEN 14, STOCKHOLM NO



ACTA OTO LARYNGOLOGICA

SUPPLEMENTUM 226

DIE MORPHOLOGIE DES GANGLION SPIRALE COCHLEAE

VON

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INHALT

I. EINLEITUNG

Die Morphologie des normalen und des pathologisch veränderten Ganglion spirale cochleae ist in den letzten Jahren aus verschiedener Sicht wiederholt untersucht worden. Die verfeinerten Methoden der modernen Morphologie ergaben eine Fülle von neuen Beobachtungen, doch fehlt bis jetzt eine Arbeit, welche diese neuern Einzelbefunde zusammenfasst. Wir stellten uns deshalb in erster Linie die Aufgabe einen Ueberblick zu geben über die jetzigen Kenntnisse vom normalen und pathologisch veränderten Spiralganglion.

Ergänzende eigene Untersuchungen sollten einerseits einige Lücken in der Morphologie des normalen Spiralganglions schliessen, anderseits aber versuchten wir anhand von Degenerationsversuchen neue Einblicke zu gewinnen in die Pathologie der ersten Neurone der Hörbahn.

II DAS NORMALE SPIRALGANGLION

A. Die peripheren cochleären Neurone

Ganglion spirale cochleae enthält die Ganglienzellen der peripheren afferenten
-one der Hörbahn Die Spiralganglienzellen sind opposito-bipolar (Schema A)
peripheren Dendriten nehmen ihren Ursprung von den kleinen wenig Synap-
-eln enthaltenden Nervenendigungen (Typ 1) an den Haarzellen des Corti'schen
-ns Sie bleiben unmyelinisiert bis nach dem Durchtritt durch die Basilarmembran
Bereich der Habenula perforata Von den *innern* Haarzellen ausgehende Den
-n verlaufen nach SPOENDLIN (88) fast ausnahmslos direkt radiär zentralwärts
-e einer Spiralganglienzelle sodass jeder innern Haarzelle mit ihren mehr als
-fferenten Nervenendigungen die gleiche Zahl von Neuronen zugeordnet wäre Es
jedoch Anhaltspunkte welche annehmen lassen dass ein Teil der von den
-rn Haarzellen herkommenden afferenten Fasern im innern Spiralbündel eine
-sse Strecke spiralig verlaufen kann (ENGSTRÖM mündl Mitteilung) Die von
äussern Haarzellen ausgehenden Fasern unterbrechen ihren radiären Verlauf
-n verschiedenen Spiralbündeln des Corti'schen Organs wobei sich von mehreren
-rzellen herkommende Fasern zu einer Faser vereinigen. Die spiralige Verlaufs-
-cke solcher Spironeurone kann 2–3 mm betragen möglicherweise kommen aber
-bei den äussern Haarzellen rein radiär laufende afferente Nervenfasern vor
Schaltungsschema und der genaue Verlauf der unmyelinisierten Dendriten sind
noch nicht in allen Teilen gesichert Besonders wäre es möglich dass noch nicht
synaptischen Kontakte entlang dieser unmyelinisierten Dendritenstrecke bekannt
. Von der Habenula perforata an sind die Dendriten myelinisiert. Sie erreichen
Spiralganglienzellen durch die Knochenkanäle der Lamina spiralis ossea In
untern Windungen wird diese Strecke annähernd radiär durchmessen gegen die
-ze der Cochlea zu erzwingt die zunehmende relative Verkürzung des Spiral
-glions einen fächerförmig ausstrahlenden, zuletzt beinahe tangentialen Faser
-auf (81) Die zentralen Axone der Spiralganglienzellen dringen bündelweise
-ch kurze Knochenkanäle und vereinigen sich im Modiolus zum N acusticus
-ei die apicalen Fasern im Zentrum des Nervenquerschnitts verbleiben. Im N
-rticus treten die Axone in dessen Gliakonus ein und teilen sich intracerebral
-otomisch. Mit Hilfe dieser Teilung gewinnt jedes Neuron sowohl im dorsalen
im *ventralen Nucleus cochlearis homolateralen synaptischen Kontakt mit den*
-ern Neuronen der Hörbahn Im Bereich der myelinisierten Dendritenstrecke an
Spiralganglienzellen und im N acusticus sind bis jetzt nie Synapsen nach
-iesen worden es scheint diese Strecke deshalb insbesondere vom feed back-System
-efferenten Fasern (olivo-cochleäres Bündel RASMUSSEN) unabhängig zu sein.

Die Zahl der peripheren cochleären Neurone lässt sich auf zwei Arten bestimmen: durch Zählung der Spiralganglienzellen (25 600–30 000 bei jungen Erwachsenen (33, 34); 40'000–50 000 bei der Katze (85, 43)) sowie durch Zählung der Nervenfasern des N. acusticus (31'000 beim Menschen (68), 5 '000 bei der Katze, 31'000 bei Affen, 24 000 bei Meerschweinchen (31)). Im Rahmen der methodischen Fehlerbreite stimmen die Zahlen überein und sind je nach Tierart 2–4 mal höher als die Zahl der Haarzellen. Die Zahl der afferenten Nervenendigungen dagegen und deren Verteilung auf die innern und äussern Haarzellen der verschiedenen Windungen ist noch weitgehend unbekannt. Die absolute Dichte der Ganglienzellen (Zellzahl pro Längeneinheit des Spiralganglions) ist gleichmässig (85), während die relative Dichte (Zahl der Spiralganglienzellen pro Längeneinheit des Corti'schen Organs) ein deutliches Maximum aufweist (34, 85). Die relative Dichte wurde als Innervationsdichte des Corti'schen Organs bezeichnet und von SCHUKNECHT (85) mit der absoluten Hörschwellenkurve verglichen. Sowohl beim Menschen wie bei der Katze verlaufen die beiden Kurven annähernd parallel, sodass die Innervationsdichte des Corti'schen Organs dessen örtliche Empfindlichkeit wiederspiegelt. Die Dichte der Spiralganglienzellen in Relation zur Dichte der Haarzellen oder der afferenten Nervenendigungen ist noch unbekannt.

Obwohl die von den äussern Haarzellen herkommenden Dendriten über eine unbekannte Strecke hin spiralig dem Corti'schen Organ entlang ziehen, wird es als gesichert erachtet, dass die verschiedenen Tonhöhen in korrespondierenden Sektoren des Corti'schen Organs und des Spiralganglions repräsentiert sind. Nur gegen den Apex zu kommt es infolge der relativen Verkürzung des Spiralganglions zu einer leichten Kompression: nach SCHUKNECHT (85) sind die apicalen 20% des Corti'schen Organs in den apicalen 10 % des Spiralganglions repräsentiert, und auch SANDO (61) kommt aufgrund seiner Experimente zu ähnlichen Schlüssen. Ueber 50 % der Neurone eines Abschnitts können ausfallen, ohne dass die Hörschwelle für die entsprechenden Frequenzen ansteigt (84, 85).

Elektrophysiologische Ableitungsversuche von Nervenfasern des N. acusticus durch TASAKI (94) ergaben, dass Neurone mit niedriger und solche mit hoher Reizschwelle unterschieden werden können, indem ein kurzes Tonsignal in den einen Fasern mit 4–6, in den andern bloss mit 1–2 Impulsen registriert wird. Es wird angenommen, die Neurone mit hoher Reizschwelle seien den innern, jene mit niedriger Reizschwelle den äussern Haarzellen zugeordnet. Aufgrund verschiedener numerischer Ueberlegungen kommt SPOENDLIN (88) zum Schluss, weitaus die Mehrzahl der peripheren Neurone der Hörbahn seien den innern Haarzellen zugeordnet. Obwohl die genauen Dendritenverläufe im Corti'schen Organ noch nicht völlig geklärt sind, wird angenommen, dass die peripheren afferenten Neurone streng entweder den äussern oder den innern Haarzellen zugehören, dass also ein Neuron nicht gleichzeitig Reize von äussern wie von innern Haarzellen empfängt. Im Spiralganglion wären demnach zwei Zellpopulationen zu unterscheiden, eine zahlenmässig vorherrschende mit hoher Reizschwelle für die innern, und eine zahlenmässig kleine mit niedriger Reizschwelle für die äussern Haarzellen.

Nach der heutigen Ansicht werden die eintreffenden Schallreize im räumlichen Gefüge des Corti'schen Organs und in dessen neuraler Schaltungsstruktur bereits wesentlich *analysiert und transformiert, bevor sie in den gegeneinander isolierten myelinisierten* Nervenfasern der peripheren Neurone den cerebralen Zentren zugeleitet werden. Nach DAVIS (10) antworten die Haarzellen auf den mechanischen Reiz der Schallwellen mit einer elektrischen Reaktion, welche ihrerseits die chemische Uebertragung auf die afferenten Nervendigungen auslöst. In den unmyelinisierten Dendriten wird der Reiz elektronisch und mit einem gewissen Dekrement weitergeleitet. Alle diese Vorgänge sind nach DAVIS graduell; erst mit dem Beginn der Myelinscheide wird die graduelle Intensitätsweiterleitung abgelöst von elektrischen Aktionspotentialen, welche dem Alles-oder-Nichts-Gesetz gehorchen und saltatorisch sich dekrementlos zentralwärts fortpflanzen. Die stufenlose Information der Schallwellen ist also in der myelinisierten Strecke der peripheren Neurone bereits in eine Folge gleichartiger, dem Alles-oder-Nichts-Gesetz unterliegender Impulse transformiert, welche nur in ihrer zeitlichen Dichte variieren. SPOENDLIN (88) vergleicht die Verhältnisse im Corti'schen Organ mit einem Analog-Rechner, während die Impulse im Bereich der myelinisierten Reizleitungsstrecke den Impulsen eines Digital-Computers entsprechen würden.

B. Die Morphologie des normalen Spiralganglion

1. *Material und Methoden*

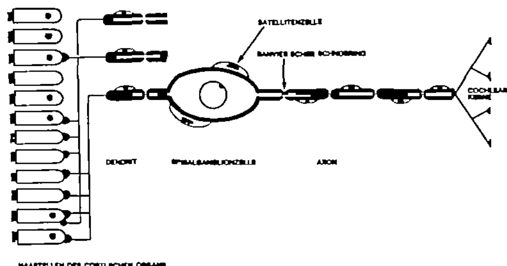
An Normaltieren wurden vor allem Meerschweinchen verwendet, vereinzelt auch Kaninchen und Affen (Saimiri sciureus). Die Tiere wurden durch Dekapitation getötet, die Schädelbasis freigelegt, die Bullae eröffnet und die Felsenbeine herausgelöst. Unter 1,5 %iger *veronalgepufferter Lösung* von Osmiumtetroxyd wurde die knöcherne Schale der Cochlea entfernt und der Modiolus im Bereich seines spiraligen Gefässkanals an mehreren Stellen perforiert. Innert wenigen Minuten erhielt so die Fixationsflüssigkeit Zutritt bis in unmittelbare Nähe des Spiralganglions. Die Präparate wurden 2 Stunden im Eiskasten belassen. Nach Auswaschen mit Ringer-Lösung wurden die Knochenblätter der Lamina spiralis ossea entfernt, bis das Spiralganglion freilag und annähernd knochensplitterfreie Segmente aus den verschiedenen Windungen herausgelöst, dehydriert und in Epoxyresin eingebettet werden konnten. Mit einem LKB-Ultrotom wurden für Phasenkontrastmikroskopie 0,5–2 μ dicke Schnitte angefertigt und mit Paraphenylendiamin (4) kontrastiert. Die Schnitte für Elektronenmikroskopie wurden teils mit Bleiacetat allein, teils kombiniert mit Bleiacetat und Uranyl kontrastiert. Betrachtung in einem Siemens-Elmiskop 1 A.

An menschlichem Material standen einige Foeten von 18–23 Wochen zur Verfügung, daneben einige Modioli (Alter 6–80 Jahre), welche 2–4 Stunden post mortem durch Osmiumperfusion durch das ovale und runde Fenster fixiert worden waren.

Vereinzelt wurde auch glutaraldehydfixiertes mit Osmiumlösung nachfixiertes und gefärbtes Material verwendet. Vergleichsweise wurden auch einige vestibuläre Ganglien von Meerschweinchen untersucht.

2. *Embryologie, Anatomie und Histologie*

Embryologisch (Literatur siehe 4, 40, 49, 91) stammen die Spiralganglienzellen wie auch die Zellen des vestibulären Ganglions aus der rostralen Wand des Gehörbläschens (10, 66). Sie vereinigen sich vorübergehend mit den Zellen des zukünftigen Ganglion geniculi zum Ganglion acustico-faciale. Bereits bei 3 Wochen alten menschlichen Embryonen sondern sich die Facialis-Ganglienzellen wieder ab, und nur das Ganglion acusticum behält seine enge Beziehung zum Gehörbläschen bei. Bei 5 mm langen Embryonen (49) entsendet der Ganglienzellhaufen die ersten Achsenzylinder und zwar zuerst peripherwärts laufende Dendriten, später die zentralwärts laufenden Axone. Das Ganglion acustico-faciale teilt sich dann in einen obern und einen untern Abschnitt. Die Hauptmasse der obern und ein Teil der untern Dendriten wenden sich den vestibulären Sinnesstellen zu, während der Rest des untern Abschnitts sich in die Konkavität des Ductus cochlearis legt und mit dessen Auswachsen die endgültige Spiralform gewinnt. Ueber den Zeitpunkt, in welchem die Dendriten bei menschlichen Embryonen die Haarzellen erreichen und die afferenten Nervenendigungen ausbilden, ist nichts Sicheres bekannt. Bei neugeborenen Mäusen sind sie vorhanden (4) und auch bei unsern 18–19 Wochen alten menschlichen Foeten



Schema A. Schematische Darstellung eines peripheren cochleären Neurons. Als Beispiele für die vorkommenden Dendritenvarianten sind zwei spiralig verlaufende (Spironeurone) und ein radiär verlaufender (Orthoneuron) Dendrit dargestellt.



Abb. 1. Corti'sches Organ eines 18–19 Wochen alten menschlichen Foetus. Mitte der Basalwindung. Nervenendigungen an den Haarzellen bei elektronenmikroskopischer Kontrolle voll ausgebildet. Grosser und kleiner Wulst noch erkennbar. Tunnel noch nicht ausgebildet. Vakuolisierung vor allem unterhalb der innern Haarzellen. Doppeltes Vas spirale. IHC = innere Haarzelle. 1 und 3 äussere Haarzellen. Phasenkontrastmikroskop 780.

waren die Nervenendigungen bei elektronenmikroskopischer Kontrolle bereits voll entwickelt. Die Myelinisation der Acusticus-Fasern wurde beim Menschen von BECHTEREW (11) beschrieben. Bei 25 cm langen Foeten werden die Fasern des N. vestibularis myelinisiert, bei 30 cm Länge diejenigen des N. cochlearis. Bei der Maus (54) werden die Dendriten und Axone der Spiralganglienzellen annähernd gleichzeitig myelinisiert, und zwar entsprechend dem allgemeinen Entwicklungsgesetz der Cochlea zuerst an der Schneckenbasis, dann langsam gegen die Spitze zu aufsteigend. Die vestibulären Fasern beginnen die Myelinisation früher als die cochleären, die cochleären schliessen sie jedoch früher ab als die vestibulären. Dementsprechend zeigten unsere jüngsten Foeten nur vereinzelt myelinisierte Fasern, bei den ältern waren die myelinisierten Fasern bereits in der Mehrzahl (Abb. 2, 3).

Nach dem Abschluss der embryologischen Entwicklung liegt das Spiralganglion allseits von dünnen Knochenlamellen umgeben im ROSENTHAL'schen Canalis spiralis



Abb. 2. Spiralganglion eines 18–19 Wochen alten menschlichen Foetus, Mitte der Basalwindung (korrespondierende Stelle zu Abb. 1). Nervenfasern fast alle noch nicht myelinisiert. Phasenkontrastmikroskop 780 ×

modioli Der Kanal besitzt keine glatten Wände sondern wird durch Knochensepten und trabekel in seinem Lumen unregelmässig eingeengt Das Ganglion bildet deshalb keinen gleichmässigen Strang, sondern weist unregelmässige Verdickungen und Einkerbungen auf. Gruppen von Ganglienzellen drängen sich in die Buchten des Kanals und in die peripher und zentralwärts sich erstreckenden Knochenkanäle für die Dendriten resp Axone der Spiralganglienzellen. Besonders beim Menschen hat das herausgelöste Ganglion den Aspekt eines unregelmässig varikösen Strangs Form und Lage des Kanalquerschnitts wechseln von Tierart zu Tierart und innerhalb einer Species von Windung zu Windung Beim Meerschweinchen liegt er relativ weit peripher in der Wurzel der Lamina spiralis ossea beim Menschen dagegen unterhalb der Ansatzlinie der Lamina spiralis ossea in einer seichten Rinne des Modiolus Die Distanz des Spiralganglions vom Corti'schen Organ nimmt entsprechend der sich verschmälernden Breite der Lamina spiralis ossea von der Basis gegen die Spitze zu ab (bei unsern Meerschweinchen von 0 8

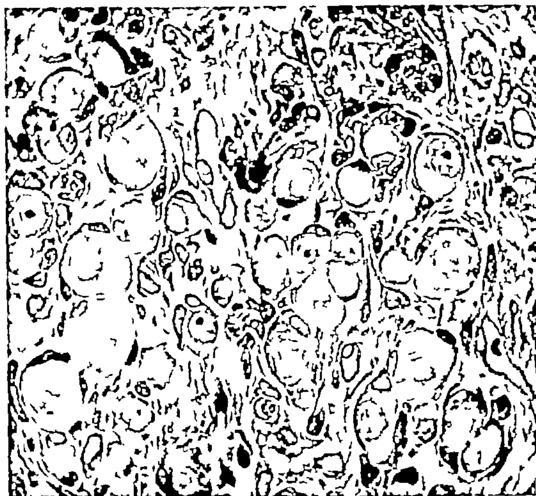


Abb. 3. Spiralganglion eines 23 Wochen alten menschlichen Foetus. Mitte der Basalwindung. Nervenfasern teilweise myeliniert. Phasenkontrastmikroskop 780 ×

mm auf 0.4 mm). Die Knochenlamelle zwischen Spiralganglion und Scala tympani ist bei Nagern dick, beim Menschen ausgesprochen dünn. Beim Menschen wird die Präparation zudem noch dadurch erleichtert, dass das Ganglion von einer kapselähnlichen dünnen Bindegewebsschicht umschlossen wird. Gegen den Apex zu nimmt die relative Verkürzung des Spiralganglions im Vergleich zur Länge der entsprechenden Abschnitte des Corti'schen Organs deutlich zu: das Ganglion bleibt gewissermassen hinter dem Corti'schen Organ zurück. Im Spitzenbereich ist es deshalb technisch schwer, sicher korrespondierende Sektoren des Corti'schen Organs und des Spiralganglions zu untersuchen.

Histologisch zeigt ein radiärer Querschnitt durch das Spiralganglion bereits bei Uebersichtsvergrösserung ein je nach Tierart verschiedenes Bild. Bei Nagern wird der ganze Querschnitt fast vollständig ausgefüllt von dicht gedrängten Ganglien

zellen und Nervenfasern. Die ovalären bipolaren Zellen sind mit ihrem längsten Durchmesser entsprechend dem vorherrschenden Faserverlauf so ausgerichtet, dass Zellen und Fasern den Querschnitt nach dem Muster von Strömungslinien ausfüllen. Nur selten werden jedoch die beiden abgebenden Fasern einer Zelle im selben Schnitt getroffen. Bei den untersuchten Affen und beim Menschen sind die Zellen zu Gruppen zusammengefasst welche besonders beim Menschen in lockerer Anordnung über den Querschnitt verstreut sind. Innerhalb der einzelnen Gruppen liegen aber auch beim Menschen die Zellen dicht gedrängt sodass sie oft einen polygonalen Querschnitt erhalten. Bei stärkerer Vergrösserung erkennt man neben den Ganglienzellen mit ihren Satellitenzellen reichlich Blutgefässe Bindegewebszellen und Nervenfasern. Ob es sich bei den im Schnitt erythrozytenfrei erscheinenden kleinsten Gefässen eventuell um Lymphgefässe handelt kann nicht entschieden werden. KOLMER (49) gibt an, die Dendriten der Ganglienzellen seien viel schmäler als die Axone In unserm Material konnten wir jedoch Axone und Dendriten im Bereich des Ganglions nicht sicher unterscheiden, erst im Bereich der Lamina spiralis ossea sind die Dendriten deutlich feiner als die Nervenfasern des Ganglions oder des N acusticus. Hingegen fallen besonders beim Meerschweinchen die intraganglionären Bündel des efferenten olivo-cochleären Systems durch einen eindeutig geringern Faserdurchmesser auf. Anhand ihres feinen Kalibers lassen sich so beim Meerschweinchen die efferenten Nervenfasern sehr leicht identifizieren. Die efferenten Bündel liegen in der Basalwindung teils im zentralen, teils im peripheren Randgebiet des Kanalquerschnitts und lassen sich bereits bei der Präparation mit Lupenvergrösserung erkennen. Zählungen ihrer myelinierten Fasern an zwei Cochleae unseres Meerschweinchenmaterials ergaben in der untern Hälfte der Basalwindung von 300 auf 500 ansteigende Zahlen, in der obern Basalwindung wird mit 500–530 das Maximum erreicht, anderthalb Windungen von der Basis enthält das nun immer peripher liegende Bündel nur noch rund 100 Fasern. In den obern Windungen sind die restlichen Fasern nicht mehr zu einem leicht erkennbaren Bündel zusammengefasst Die erhaltenen Zahlen stimmen überein mit der Tatsache (67 62) dass die rund 500 Fasern des efferenten Bündels im Bereich der obern Basalwindung ins Ganglion eintreten und sich von dort aus teils basalwärts, teils apicalwärts wenden. Besonders im Bereich der intraganglionären Spiralbündel erkennt man bei starker Vergrösserung auch Bündel unmyelinierter Fasern von wechselndem Durchmesser Eindruckmässig scheint ihre Zahl bei den untersuchten Affen und beim Menschen höher zu sein als beim Meerschweinchen, genaue Zählungen waren jedoch in unserm Material nicht möglich. Herkunft und Ziel dieser unmyelinierten Fasern sind unsicher Möglicherweise erreichen sie das Spiralganglion mit den afferenten Fasern des N acusticus und setzen sich fort in den adrenergischen Plexus (90) der Lamina spiralis ossea Im Bereich des Spiralganglions treten sie in unserm Material nirgends in nähere Beziehung zu den Gefässen.

Die Spiralganglienzellen selbst haben eine ovaläre Gestalt, welche sie nur dann verlieren, wenn sie so dicht gedrängt liegen, dass polygonale Querschnitte erzwungen werden. Ihre Grösse wurde bei verschiedenen Tierarten und beim Menschen von

ALEXANDER (1) und MÜNZER (59) angegeben. In unserm Material fanden wir durchschnittliche längste Durchmesser von 22μ für Meerschweinchen und Kaninchen, 20μ bei Saimiri sciureus und 25–30μ beim erwachsenen Menschen. Sowohl beim Meerschweinchen wie beim Menschen lassen sich anhand der Grösse zahlenmässig unbedeutende Gruppen mit eindeutig geringerem Durchmesser abgrenzen (10μ beim Meerschweinchen 10–15μ beim Menschen) Bereits ALEXANDER (1) hat darauf hingewiesen dass die Zellgrösse im Spiralganglion bei allen Tierarten viel weniger schwankt als in den vestibulären Ganglien Auch die Nervenfasern weisen im Bereich des Spiralganglions eine viel geringere Dickenvariation auf als im Vestibularganglion (in unserm Material beobachteten wir im vestibulären Ganglion des Meerschweinchens oft Faserdurchmesser von 10–20μ im Spiralganglion nie über 8μ)

*Im osmiumfixierten Material lässt sich leicht erkennen dass die meisten Spiral*ganglienzellen von einer Myelinhülle umgeben sind welche sich als schwarzes Band kontinuierlich von den beiden Faserfortsätzen über die Nervenzelle hinzieht „Markhaltige Ganglienzellen wurden 1851 von LEYDIG (53) erstmals beschrieben Ihre Existenz blieb aber jahrzehntelang umstritten Bei Säugern wurden solche Zellen erstmals von WITTMAACK (99) in Spiralganglien nachgewiesen, später fand man sie ausserdem noch im vestibulären vereinzelt auch noch in Trigeminus- und Vagusganglien MÜNZER (59) studierte später eingehend die Verbreitung myelinierter und unmyelinierter Zellen in den Hirnnervenganglien verschiedener Tierarten. Der Begriff der myelinierten afferenten Ganglienzellen fand aber nur sehr langsam Eingang in die Literatur und als er sich endlich durchgesetzt hatte waren die genauen Angaben der ursprünglichen Arbeiten in Vergessenheit geraten Es wurde nun kurzerhand angenommen, alle Zellen der Octavus-Ganglien seien bei Säugern *myeliniert So konnte in den letzten Jahren verschiedentlich die Tatsache entdeckt* werden dass zumindest beim Meerschweinchen auch unmyelinierte Spiralganglienzellen vorkommen (70 93 95) Unmyelinierte Zellen des Meerschweinchenspiralganglions wurden jedoch bereits von MÜNZER erwähnt indem er richtig angibt, sie bilden die Ausnahme unter den vorherrschenden myelinierten Zellen NISHIMURA *et al* (61) geben an sie hätten unmyelinierte Zellen nur bei einem Teil ihrer Meerschweinchen finden können, in seltenen Ausnahmefällen erreiche ihr Prozentsatz 10 %. Wir konnten jedoch phasenkontrastmikroskopisch bei allen unsern Meerschweinchen und in allen Windungen des Spiralganglions solche unmyelinierten Zellen finden (Abb 4) Sie liegen vorwiegend im peripheren Teil des Ganglions, oft gehäuft in der Nähe der intraganglionären Spiralbündel häufig finden sie sich aber auch zentralwärts zwischen den zum N acusticus laufenden Axonen. Im Zentrum des Ganglionquerschnitts sind sie nur vereinzelt anzutreffen. Sie ent*sprechen der oben beschriebenen Gruppe der kleinen Zellen des* Meerschweinchenspiralganglions Ihr Plasma ist heller als dasjenige der myelinierten Zellen Ihr Kern weist einen meist zentral gelegenen, grossen Nucleolus auf Für Zählungen der unmyelinierten Zellen muss berücksichtigt werden, dass sie nicht gleichmässig über den Ganglionquerschnitt verteilt sind es kann deshalb nur eine genau radiäre Schnittebene, welche auch die peripheren Teile des Ganglions sicher miterfasst ein

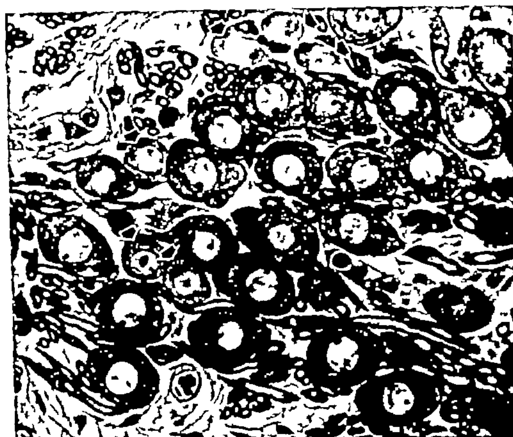


Abb. 4. Spiralganglion Meerschweinchen, radiärer Querschnitt 2 Windungen von der Basis. In der Peripherie (Pfeile) erkennt man mehrere unmyelinisierte, kleinere Ganglienzellen mit helleren Zytoplasma. Randständigkeit der Nucleoli bei den myelinisierten Ganglienzellen. Phasenkontrastmikroskop 780 ×

repräsentatives Verhältnis zwischen den beiden Zellarten ergeben. Bei unsern Zählungen berücksichtigten wir zudem bei beiden Zelltypen nur jene Zellen, bei welchen ein Nucleolus im Schnitt getroffen war. So konnte die unterschiedliche Zellgrösse ungefähr kompensiert werden. Bei grossen Schwankungen von Schnitt fanden wir bei allen Tieren und in allen Windungssektoren einen Prozentsatz von 10% unmyelinierter Zellen.

Die elektronenmikroskopischen Arbeiten der letzten Jahre liessen erkennen, dass die Myelinhülle im Phasenkontrastmikroskop nicht in jedem Fall zuverlässig beurteilt werden kann. MÜNZNER (59) Angaben müssen deshalb in verschiedenen Punkten berichtigt werden. Das phasenkontrastmikroskopische Bild der Myelinhülle und der Satellitenzellen soll deshalb erst im folgenden Abschnitt besprochen und mit den elektronenmikroskopischen Befunden verglichen werden. Auch in den Nerven-

zellen des Spiralganglions lassen sich zwar im Phasenkontrastmikroskop viele Einzelheiten erkennen, doch gilt auch hier, dass sie nur bei gleichzeitiger elektronenmikroskopischer Kontrolle richtig interpretiert werden können. Das phasenkontrastmikroskopische Bild der Ganglienzellkörper soll deshalb ebenfalls erst im folgenden Abschnitt zusammen mit den elektronenmikroskopischen Befunden besprochen werden.

3 *Die Feinstruktur der Ganglienzellen und ihrer Hülle*

Die Feinstruktur myelinierter akustischer Ganglienzellen wurde erstmals von ROSENBLUTH und PALAY (77) bearbeitet. Sie beschrieben das phasenkontrastmikroskopische und elektronenmikroskopische Bild der Ganglienzellen des achten Hirnnerven bei Goldfischen. Später folgte eine Arbeit von ROSENBLUTH über die Zellen der akustischen Ganglien der Ratte (74), wobei besonders eingehend Probleme der Myelinhülle behandelt wurden. Japanische Autoren (61, 93) gaben die ersten elektronenmikroskopischen Beschreibungen der Spiralganglienzellen bei Meerschweinchen und Kaninchen, und kürzlich erschienen von REINECKE (69, 70) zwei Arbeiten über die Spiralganglienzellen bei menschlichen Foeten und beim Meerschweinchen. Für die Beurteilung der Feinstruktur der Ganglienzellkörper erwies es sich als nützlich, die Studien von CERVÓS-NAVARRO (15) und ANDRES (5) über die Spinalganglienzellen vergleichsweise heranzuziehen.

a *Kern*

Phasenkontrastmikroskopisch zeigt der Kern bei allen bis jetzt untersuchten Tierarten eine annähernd zentrale Lage. Nur in unserm erwachsenen menschlichen Material fanden wir recht häufig stark periphere Kerne, möglicherweise jedoch infolge postmortaler Veränderungen. Mit Ausnahme vereinzelter Zellen beim Menschen (10?) kommt der Kern nur in der Einzahl vor. In unserm menschlichen Material sahen wir nur zweimal eine sicher zweikernige Zelle. Die Kontur der recht grossen Kerne (9–10μ beim Meerschweinchen, Saimiri sciureus und Kaninchen, 10–11μ beim Menschen) ist meist kreisrund, doch finden sich immer wieder Kerne mit gewellter oder sogar tief eingebuchteter Kernmembran. Nach WÜSTENFELD und HALBFAS (103) nimmt die mittlere Kerngrösse beim Meerschweinchen in basoapicaler Richtung signifikant um etwa 1μ zu. Im osmiumfixierten Material sind die Kerne heller als die Perikarya, sie zeigen eine lockere Chromatinstruktur, von welcher die bei allen untersuchten Tierarten in der Mehrzahl vorkommenden Nucleoli sich stark abheben. Beim Meerschweinchen liegen weniger als die Hälfte der Nucleoli zentral, mehr als die Hälfte berührt die Kernmembran oder sitzt ihr sogar breitbasig auf. Nur die kleinen unmyelinierten Zellen zeigen fast ausnahmslos einen zentral gelegenen Nucleolus von 2,5–3μ Durchmesser, während die Nucleoli der myelinierten Zellen selten grösser sind als 2μ. Auch beim Kaninchen, bei den untersuchten Affen und beim Menschen überwiegen die zentral gelegenen Nucleoli bei weitem. Als dunkelgraue Masse erkennt man sehr häufig dem Nucleolus anliegend einen Nucleolarsatelliten (nucleolus-associated heterochromatin).

Elektronenmikroskopisch ist der Kern von einer doppeltkonturierten Membran umgeben, deren Spaltraum in Verbindung steht mit dem Spaltensystem des endoplasmatischen Reticulums. In unregelmässigen Abständen finden sich Kernporen. Der Kerninhalt erscheint auch im Elektronenmikroskop hell, von gleichmässig granulierter bis kurz filamentöser Struktur. Die Kernform ist im Schnitt häufig prall kreisrund, häufig aber auch gewellt, wobei die Wellung manchmal auffallend regelmässig sich über den Umfang des Kerns hinzieht. Glatt konturierte und über den ganzen Umfang mehr oder weniger gewellte Kerne sind häufiger als gemischte Uebergangsformen. Die Nucleoli lassen im Elektronmikroskop das knäuelartige Gerüst der Nucleolonemata erkennen, der Nucleolarsatellit liegt dem Nucleolus an als gleichmässig granulierte, unscharf begrenzte und weniger elektronendichte Masse.

b. *Perikarya*

Im Phasenkontrastmikroskop sind die Perikarya der kleinen unmyelinierten Zellen des Meerschweinchenspiralganglions viel heller als diejenigen der myelinierten Zellen. Bei den andern untersuchten Tierarten liessen sich phasenkontrastmikroskopisch keine entsprechenden Perikaryon-Typen unterscheiden. Die Nissl-Schollen lassen sich im osmiumfixierten Material nicht so leicht abgrenzen wie in den üblichen Nissl-Färbungen, sie bilden annähernd homogene, graue Schollen, welche sich nur schwach von den übrigen Abschnitten der Perikarya abheben. Dagegen erkennt man jene Zonen gut, welche vorwiegend Neurofilamente enthalten. Sie erscheinen im Phasenkontrastmikroskop als praktisch leere, helle Strassen.

Bei allen untersuchten Species finden sich in wechselnder Menge stark osmiophile Granula, welche als Pigmentgranula bezeichnet werden. Sie weisen jedoch in ungefärbtem, glutaraldehyd- oder formalinfixiertem Material nur eine kaum wahrnehmbare gelbliche Eigenfarbe auf. Die Menge dieser osmiophilen Körner ist starken individuellen Schwankungen unterworfen. Beim Meerschweinchen können die einzelnen Granula weit über ein μ messen, oft sind sie zu Gruppen oder Rosetten zusammengefasst. Bei den untersuchten Affen und beim Kaninchen sind die Granula feiner und diffus verteilt. Beim Menschen sind die bald staubförmigen, bald bis rund 1μ messenden Granula meist peripher angeordnet. Unsere menschlichen Foeten enthielten praktisch keine solchen osmiophilen Partikel, jugendliche Erwachsene nur vereinzelte, ältere Erwachsene dagegen zeigen regelmässig zahlreichere und grössere Granula.

Beim Meerschweinchen erkennt man oft mehrere μ grosse, polymorphe und wechselnd stark osmiophile Körper, welche bereits im Phasenkontrastmikroskop deutlich geschichtet erscheinen und meist im Bereich der Faserabgänge vorkommen. Die Zahl und Grösse dieser Einschlüsse ist ebenfalls starken individuellen Schwankungen unterworfen.

Elektronenmikroskopisch entspricht der Feinbau der Spiralganglien-Perikarya weitgehend dem Bild, wie es bei den Zellen der Spinalganglien beschrieben wurde. Die Zellmembran liegt normalerweise der umgebenden Satellitenzellhülle dicht an.

Unter dem Plasmalemma hat ROSENBLUTH (74 75) „subsurface cisterns" besch welche bei Zellen mit lockerem Myelin häufiger sind als bei solchen mit kom Myelinhülle (über die Myelintypen siehe weiter unten) Ebensolche Zistern REINECKE (69) auch an Spiralganglienzellen menschlicher Foeten nachgewie Zytoplasma werden nach NISHIMURA *et al.* (61) zwei Arten von feinen G unterschieden Die einen entsprechen Ribosomen, die andern, etwas gr werden als Glykogengranula angesprochen Im endoplasmatischen Reticulum die ribosomenbesetzten Spalträume oft wirbelähnliche Strukturen (Abb 6) I mit den zwischen den Spalträumen liegenden Teilen der zytoplasmatischen das elektronenmikroskopische Substrat der lichtmikroskopischen Nissl-Schol (20 44 65) Golgi Zonen befinden sich ohne besonders bevorzugte Lage ver ganzen Zytoplasma Die Mitochondrien zeigen oft eine unregelmässige Fo sammeln sich häufig an im Bereich der Faserabgänge Ihre Matrix ist viel h die elektronendichte Matrix der Satellitenzellmitochondrien (61) Neurofilamen in wechselndem Ausmass verteilt über die Zelle sie sind meist in Strassen ange welche sich im Abgangskegel der Achsenzylinder sammeln und kontinuie die Achsenzylinder der abgehenden Dendriten und Axone übergehen

In Bezug auf die Feinstruktur lassen sich bei verschiedenen Tierarten zwei unterscheiden. beim filamentösen Typ überwiegen die Neurofilamente beim lären die Ribosomen, das endoplasmatische Reticulum und die Mitocho weshalb beim zweiten Typ das Perikaryon als Ganzes elektronendichter er Die beiden Typen entsprechen bis zu einem gewissen Grad den beiden Haup der Spinalganglienzellen wie sie von ANDRES (5) elektronenmikroskopisch besc wurden. Der granuläre Typ lässt sich vergleichen mit dem Spinalganglienzel der filamentöse mit dem Typ A im Spinalganglion. Beim Meerschweinchen s kleinen unmyelinierten Zellen dem filamentösen Typ zuzuordnen die myeli Zellen dem granulären Typ (61 70) Beide Perikaryon Typen wurden von I BLUTH und PALAY (77) sowie ROSENBLUTH (74) auch bei Goldfischen und I unterschieden während wir beim Kaninchen und Saimiri sciureus keine eind Perikaryon-Typen abgrenzen konnten.

Wie in den andern Nervenzellen finden sich auch in den Spiralganglienpe verschiedene Arten von *Einschluss korpern*. Ihre Nomenklatur ist verwirren lange Liste der bis jetzt geprägten Bezeichnungen lässt darauf schliessen, d jetzt noch kein befriedigendes Einteilungsprinzip gefunden wurde Dense *bo* bodies, pigment granules capsulated and uncapsulated small bodies, heterog bodies cytolysomes, multicystic cystosomes, microbodies liposomes, osm Zytosomen, Lamellenkörperchen, inclusion bodies resembling early myelin sh myelin figures — dies sind nur einige der Bezeichnungen aus der elektronen skopischen Literatur über Ganglienzellen. Aus der Liste geht auch hervor da deskriptive Kriterien und funktionelle Deutungen gemischt zur Bezeichnun wendet werden. MAUNSBACH (56) versuchte kürzlich eine Systematik de schlusskörper aufzustellen, wobei er sich vor allem auf den Charakter od Fehlen einer Membran stützte Seine Arbeit beruht auf Untersuchungen a

Rattenniere: er äusserte aber die Hoffnung sein Schema lasse sich auch auf andere Zellarten übertragen. Leider ist es uns nicht gelungen, seine Einteilungsprinzipien auf die Polymorphie der Einschlüsse in den Spiralganglienzellen anzuwenden. Auch die kürzlich von REINECKE (70) an Spiralganglienzellen des Meerschweinchens aufgestellten drei Gruppen von Einschlusskörpern sind zu wenig klar definiert, als dass sie als Grundlage eines Einteilungsschemas verwendet werden könnten. Wir möchten deshalb aus dem Spektrum der polymorphen Einschlüsse bloss drei Gruppen hervorheben, welche jedoch durch mannigfache Uebergangsformen ineinander übergehen. Solche Übergangsformen lassen vorderhand noch alle Einteilungskriterien willkürlich erscheinen. Am leichtesten sind die *Pigmenteinschlüsse* zu erkennen. Es handelt sich dabei um meist rundliche ein oder mehrere μ erreichende elektronendichte Körperchen mit einfacher oder doppelter Membran und gleichmässig granuliertem oder auch geschichtetem Inhalt hie und da auch mit vakuolenartigen Aufhellungen. In seltenen Fällen fanden wir auch bei Normaltieren Bilder wie sie die Abb 18 bei einem knallexponierten Tier wiedergibt. Obwohl diese Partikel in ungefärbtem Material lichtmikroskopisch nur eine kaum wahrnehmbare Eigenfarbe aufweisen, sind sich doch alle Untersucher darin einig dass sie aufgrund ihrer Ultrastruktur und ihres färberischen Verhaltens den Lipofuscineinschlüssen anderer Zellen entsprechen müssen. In unserm menschlichen Material nahm die Zahl und Grösse dieser osmiophilen Partikel mit dem Alter zu, was sich mit der Annahme vereinbaren lässt, dass solche Einschlüsse als „Abnützungspigment" zu gelten haben.

Hie und da enthalten die Pigmentkörperchen nicht nur konzentrisch geschichtetes Material verschiedener Elektronendichte, sondern auch Strukturen, welche manchmal als Reste von Zellorganellen identifiziert werden können. Damit bestehen fliessende Uebergänge zur zweiten Gruppe von Einschlüssen, welche in grosser Variabilität geformtes und ungeformtes Material in sich einschliessen und als *Lysosome* gedeutet werden, also als Verdauungs- oder Sequestrierungsorganellen der Zelle für unbrauchbares Material. Die Lysosome sind immer von einer deutlichen Membran umschlossen, welche oft myelinähnlich regelmässig geschichtet ist. In diesem Fall können sie oft kaum mehr unterschieden werden von Einstülpungen oder abgeschnürten Teilen der wirklichen Myelinhülle. Auf diese *myelinierten Einschlüsse* soll weiter unten genauer eingegangen werden.

Die Zuteilung der einzelnen Einschlusskörper zur einen oder andern Gruppe wird nur durch verfeinerte histochemische Methoden der Elektronenmikroskopie möglich werden (Lipidnachweis und -analyse im Falle der Pigmentgranula. Nachweis der sauren Phosphatase und anderer Fermente im Falle der Lysosome). Herkunft und Entwicklung der verschiedenen Einschlüsse sind schwer abzuschätzen da die Elektronenmikroskopie ja nur Momentaufnahmen geben kann. Als mögliche Ursprünge werden verschiedene Zellorganellen in Betracht gezogen (Mitochondrien, endoplasmatisches Reticulum, Golgi Vakuolen). Ebenso ist vorderhand nicht klar ob sämtliche Einschlüsse als pathologisch zu gelten haben. Es ist nur bekannt, dass sie an Zahl, Grösse und Polymorphie in geschädigten Ganglienzellen zunehmen (7 29 4., 57)

c *Satellitenzellhülle*

Die Myelinhülle der Spiralganglienzellen zeigt sich im Phasenkontrastmikroskop als dickeres (bis 1μ beim Meerschweinchen) oder dünneres (0,3μ beim Menschen) homogenes Band von wechselnd intensivem Schwarz. Nur selten sind Aufsplitterungen in Teilschichten erkennbar, besonders im Bereich der Faserabgänge. Es könnte sich aber in diesen Fällen um Artefakte durch Fixation und Dehydration handeln. Beim Meerschweinchen und beim Kaninchen sowie bei Saimiri sciureus sind die Myelinhüllen der einzelnen Zellen immer voneinander getrennt, während beim Menschen die zarten Hüllen benachbarter Zellen phasenkontrastmikroskopisch zusammenfliessen können, sodass der Eindruck einer gemeinsamen Hülle um mehrere Zellen entsteht. Die unmyelinierten Zellen des Meerschweinchens sind nur von einer kaum wahrnehmbaren feinsten grauen Linie begrenzt, welche der zytoplasmatischen Schicht der Satellitenzelle entspricht. Bei den myelinierten Zellen setzt sich die Hülle ohne Unterbruch auf die Achsenzylinder der Dendriten und Axone fort. Sie wird erst unterbrochen an den Ranvier'schen Schnürringen, welche meist etwa 20μ vom Abgang der Achsenzylinder entfernt liegen. Die Ganglienzelle ist demnach eingeschlossen in die Mitte eines internodären Segments des Neurons. Bereits im Phasenkontrastmikroskop lässt sich erkennen, dass die Myelinhülle dieses Segments weniger dicht durch Osmium geschwärzt wird als im Bereich der anschliessenden Nervenfasersegmente. Die an die Ganglienzelle anschliessenden ersten Ranvier'schen Schnürringe erscheinen deshalb in dem Sinne asymmetrisch, dass mühelos die der Zelle zugewandte Seite mit ihrer grauen Myelinhülle von der der Zelle abgewandten Hälfte mit dicht schwarzer Hülle unterschieden werden kann (Abb. 10). Häufig ist die Myelinhülle im Bereich der Faserabgänge gewellt, manchmal erkennt man sogar anscheinend isolierte myelinierte Körper, welche mehrere μ gross werden können und frei im Perikaryon der Ganglienzelle zu liegen scheinen. Besonders beim Meerschweinchen sind solche myelinierten Körper häufig.

Die Satellitenzellen sind meist in der Mehrzahl vorhanden, doch haben wir in unserm Material bei einer Schnittdicke von maximal 2μ nie mehr als drei Satellitenzellkerne an einer Ganglienzelle gesehen. Die Anordnung der kernführenden Ausbuchtung der Satellitenzelle in Bezug auf die Faserabgangsstellen der Ganglienzelle ist bei den von uns untersuchten Species regellos, während ROSENBLUTH und PALAY (77) bei Goldfischen beobachteten, dass die Satellitenzellkerne sich vorwiegend in den Winkel zwischen Zellkörper und Faserabgang einfügen. Der Satellitenzellkern ist langgestreckt ovalär, selten nierenförmig mit seichter bis tiefer Einschnürung. Er enthält 1–3 Nucleoli. Auch ausserhalb der kernführenden Anschwellung der Satellitenzelle sind entlang dem Ganglienzellumfang immer wieder schmale Zytoplasmasäume erkennbar, welche sich vor allem durch dunkle, langgestreckte Körper auszeichnen. Es entsprechen diese Körper den auch elektronenmikroskopisch auffallend dichten Mitochondrien der Satellitenzelle.

Seit den grundlegenden elektronenmikroskopischen Arbeiten von GEREN (32) und ROBERTSON (72) ist bekannt, dass die Myelinhülle der myelinierten Nervenfasern aus spiralig sich um den Achsenzylinder legenden Schichten der Satelliten

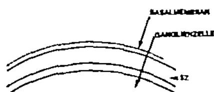


Abb. 5. Myelinierte Spiralganglionzelle eines normalen Meerschweinchens, Basalwindung. Zwei randständige Nucleolarapparate. Granulärer Perikaryon-Typ mit reichlich Mitochondrien, Golgi Zonen (G), endoplasmatischem Reticulum und Pigmentkörpern. Der kreisrunde Einschluss oben rechts ist von einer Vervierfachung der Myelinhülle umgeben. Die Aussenseite der Myelinhülle ist beim äussersten und beim zweitinnersten der konzentrischen Ringe gegen das Zentrum zu gerichtet, beim innersten und beim zweitäussersten vom Zentrum der Formation weg, sodass es sich um eine teleskopartige Einstülpung der Myelinhülle (M) handeln könnte, eventuell aber bereits mit echter Abschnürung von konzentrischen Myelinkugeln. Elektronenmikroskop, Markierung = 1µ (ebenso in allen folgenden elektronenmikroskopischen Abbildungen)

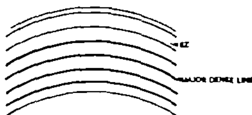


Abb. 6 Myelinisierte Spiralganglienzelle (Meerschweinchen). Parallele Ausrichtung der Spalten des endoplasmatischen Reticulums mit angedeuteter Wirbelbildung. Mvb = multivesicular body

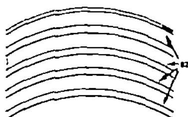
TYPEN DER SATELLITEN ZELLHÜLLE



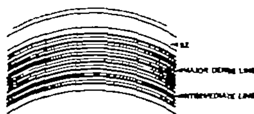
EINE ZYTOPLASMATISCHE LAGE



SEMIKOMPAKTES MYELIN



MEHRERE ZYTOPLASMATISCHE LAGEN



KOMPAKTES MYELIN

Schema B. Schematische Darstellung der Myelintypen. Eine zytoplasmatische Lage = unmyelinisiert, mehrere zytoplasmatische Schichten = lockeres Myelin. SZ = zytoplasmatische Schicht der Satellitenzelle

zelle besteht. Im Laufe des Umwicklungsprozesses verschmelzen die ursprünglich zytoplasmatischen Schichten zu einem Spiralsystem, welches aus radiär strukturierten Lipid- und tangential strukturierten Proteinschichten aufgebaut ist. Die ursprünglichen zytoplasmatischen Schichten sind beidseits von der Zellmembran begrenzt („unit membrane"), welche ihrerseits aus drei Einzelschichten aufgebaut ist. Die beiden innern Lagen der „unit membranes" einer zytoplasmatischen Satellitenzellschicht verschmelzen zu einer „major dense line", während die äussern Lagen der „unit membranes" zweier benachbarter zytoplasmatischer Satellitenzellschichten sich zwischen den beiden „major dense lines" zur „intermediate line" vereinigen. Am äussern Ende öffnet sich die Spirale zum äussern, am innern Ende zum innern Mesaxon (Abb. 9). Der Lipidgehalt der Myelinscheide ist verantwortlich für die Osmiophilie, der streng ausgerichtete molekuläre Bau mit seiner regelmässigen Periodizität für die optische und röntgenologische Doppelbrechung. Auch bei der Myelinhülle der Ganglienzellen wird angenommen, dass sie durch progressive Umhüllung vorerst zytoplasmatischer Lagen der Satellitenzelle zustande kommt. Ona (64) konnte den Umwicklungsprozess an Kulturen akustischer Ganglienzellen von Hühnerembryonen direkt beobachten.

Die Arbeiten von ROSENBLUTH und PALAY (77) sowie von ROSENBLUTH (74) lassen an myelinisierten Ganglienzellen drei Arten von Myelin unterscheiden (Schema B): kompaktes, semikompaktes und lockeres Myelin. Das kompakte Myelin besteht

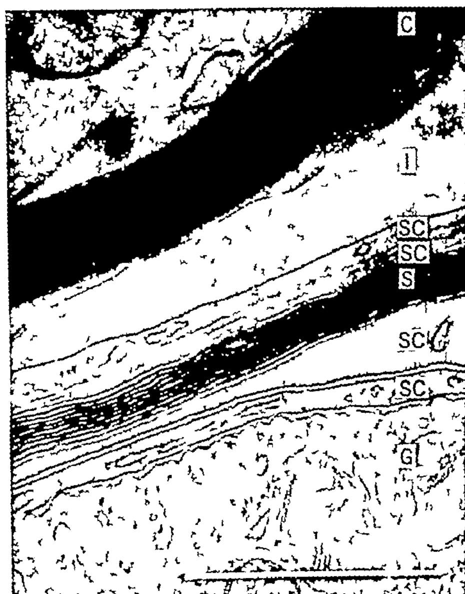


Abb. 7. Myelinhülle einer Nervenfaser (oben) und einer Spiralganglienzelle (unten). Die Myelinhülle der Nervenfaser besteht aus kompaktem Myelin (C) mit 22 major dense lines, die Hülle der Ganglienzelle von innen nach aussen aus zwei zytoplasmatischen (SC) Schichten, 8 Schichten semikompakten Myelin (S) und äussern zytoplasmatischen Schichten (SC). Periodizität des semikompakten Myelins doppelt so gross wie beim kompakten Myelin. G = Perikaryon der Ganglienzelle. I = Interzellularraum. Meerschweinchen, Elektronenmikroskop.



Abb. 8 Myelinhüllen zweier benachbarter Spiralganglienzellen (Meerschweinchen). Beide Hüllen weisen 15 Schichten auf G = Perikaryon der Ganglienzelle M = lockere und semikompakte Myelinschichten, SC = äusserste zytoplasmatische Schicht der Satellitenzelle I = interstitieller Raum, gegen Neuron zu begrenzt von feiner Basalmembran.

zu dicht gelagerten „major dense lines" (Periodizität 115 Å beim Goldfisch, 150 Å bei der Ratte) deren helle Zwischenzone durch eine intermediäre Linie unterteilt wird. Das kompakte Myelin entspricht in seinem Aufbau der Myelinscheide myelinisierter Nervenfasern. Semikompaktes Myelin besteht ebenfalls aus „major dense lines", es fehlen jedoch intermediäre Linien. Zudem ist die Periodizität mit rund 200 Å doppelt so gross wie beim kompakten Myelin (Abb 7) Lockeres Myelin besteht aus zytoplasmatischen Lagen zur Satellitenzelle Deren Abstand kann sich

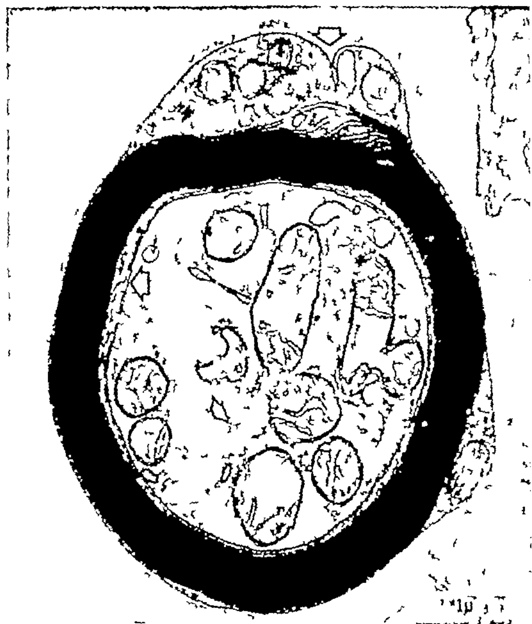


Abb. 9 Myelinisierte Nervenfaser im Meerschweinchenspiralganglion. 21 major dense lines, innerste und äusserst Schicht der Hülle zytoplasmatisch. Man erkennt das innere und äussere Mesaxon (Pfeile). Elektronenmikroskop.

jedoch soweit verringern dass stellenweise ebenfalls intermediäre Linien gebildet werden. Bei weiterer Annäherung können die einander zugekehrten Plasmamembranen zweier Satellitenzellschichten zu einer gemeinsamen unit membrane verschmelzen.

Entlang dem Umfang einer Ganglienzelle kann sich der Charakter der Myelinhülle mehrmals ändern. Lockere zytoplasmatische Schichten können zu „major dense lines" verschmelzen und kompaktes oder semikompaktes Myelin bilden, einzelne Schichten können auch mit kleinen plasmagefüllten Schlingen blind endigen. Auch von innen nach aussen gesehen ist die Myelinhülle kaum je einheitlich aufgebaut (Abb 8) In wechselnder Zahl lösen sich kompakte semikompakte und lockere Schichten ab Zuäusserst folgt immer eine zytoplasmatische Schicht welche sich zur Aufnahme des Satellitenzellkerns erweitert und irgendwo am äussern Umfang der Ganglienzelle blind endigt (äusseres Mesaxon) Entsprechend lässt sich am innern Ende der Spirale das innere Mesaxon auch bei Ganglienzellen erkennen. Die im einzelnen nie einheitliche Myelinhülle der Ganglienzellen kann so nur nach dem vorherrschenden Typ als kompakt semikompakt oder locker bezeichnet werden. Kompaktes Myelin ist bis jetzt nur bei Goldfischen und vereinzelt auch bei der Ratte nachgewiesen worden, nie bei den übrigen der bis jetzt untersuchten Species. Die Zahl der Schichten wechselt auch innerhalb einer Tierart von Zelle zu Zelle sehr stark, im Mittel werden für Goldfische bei lockeren Myelinhüllen 2–30 Lagen, bei kompakten Hüllen 10–00 Lagen angegeben, bei Ratten rund 10 bei Meerschweinchen 12–18 Die Zahl der Schichten um die Ganglienzellen ist immer geringer als in den Myelinscheiden der angrenzenden Nervenfasersegmente. NISHIMURA *et al* (61) geben zudem an, die Zahl der Schichten nehme beim Meerschweinchen regelmässig von der Zelle gegen die Faserabgänge ab eine Beobachtung die wir in unserm Material nicht konstant bestätigt fanden. Die Schichten sollen hie und da durch desmosomenartige Strukturen untereinander verbunden sein (74) Ranvier sche Schnürringe und Schmidt Lanterman sche Einkerbungen wurden an den Hüllen der Ganglienzellen nie beobachtet. In unserm Meerschweinchenmaterial fanden wir jedoch mehrmals Zellen, bei denen der anschliessende erste Ranvier sche Schnürring so dicht am Faserabgang sass, dass seine eine Hälfte gleichsam auf die Zelle aufgerutscht erschien. Sehr häufig fanden wir auch schräg von innen nach aussen verlaufende Kolonnen von kleinen, spindelförmigen zytoplasmahaltigen Aufspaltungen der „major dense lines" welche durchaus den von ROBERTSON (73) an peripheren Nervenfasern als Schmidt Lanterman sche Einkerbungen bezeichneten Strukturen entsprechen. Die Myelinhülle wird vom Interzellulärraum getrennt durch eine flaue Basalmembran („external lamina nach FAWCETT (26)) welche sich ohne Unterbrechung über die ganze Zelle, aber auch über die Ranvier schen Schnürringe der abgehenden Nervenfasern hinzieht.

ROSENBLUTH (74) hat auf die Schwierigkeiten hingewiesen, eine sichere Grenze zu ziehen zwischen myelinierten und unmyelinierten Ganglienzellen. Er verweist auf SCHMITT (83) welcher auf ähnliche Definitionsschwierigkeiten bei den Nervenfasern aufmerksam machte. ROSENBLUTH setzte als Definition fest, er betrachte alle Zellen

als myelinisiert, sobald sie von mehr als einer einzigen Satellitenzellschicht umgeben seien, unabhängig davon, ob es sich um »major dense lines» oder bloss um zytoplasmatische Schichten handle. HESS (30) übernahm in einer Arbeit über myelinisierte Ganglienzellen im Ciliarganglion von Hühnern ROSENBLUTHS Definition mit der Einschränkung, dass er eine rein aus zytoplasmatischen Schichten aufgebaute Hülle nur dann als myelinisiert bezeichnet, wenn mehrere solche Lagen vorhanden sind und sie eine regelmässige Periodizität aufweisen. Da aber die Fusion der zytoplasmatischen Schichten zu »major dense lines» unseres Erachtens doch zum Begriff Myelin gehört, bezeichnen wir in der vorliegenden Arbeit alle Zellen als myelinisiert, welche zumindest über einen Teil ihres Umfanges eine oder mehrere »major dense lines» aufweisen, unabhängig von der Zahl der Schichten.

Jede myelinisierte Ganglienzelle weist in ihrer Scheide eine Fülle von Unregelmässigkeiten auf. Nicht nur wechseln Zahl und Charakter der Schichten andauernd, manche Schichten endigen auch blind oder wenden sich sogar nach rückwärts. Auch findet sich oft mehr als ein inneres oder äusseres Mesaxon. Die Hülle als Ganzes liegt oft der Zelle nicht glatt an, sondern bietet einen welligen Aspekt mit mäanderartigem Schnittverlauf, wie wenn sie zuweit wäre für die Grösse der Zelle. Je nach der Schnittrichtung erscheinen solche Einstülpungen als Mehrzahl konzentrischer Myelinringe im Zwischenraum zwischen Zelle und der durchgehenden äussern Myelinscheide (Abb. 8). Durch Zählung der Schichten lässt sich oft sichern, *dass es sich um die gleiche Myelinhülle handeln muss; es kann aber nicht immer* ausgemacht werden, ob es sich um teleskopartige Einstülpungen oder um wirklich abgeschnürte Myelinkugeln handelt. Solche myelinisierte Einschlüsse haben wir elektronenmikroskopisch nur eingebettet im Zytoplasma der Satellitenzelle oder im Spaltraum zwischen Ganglienzelle und Myelinhülle gefunden, nie jedoch in den Perikarya der Ganglienzellen, wie es im Phasenkontrastmikroskop oft den Anschein hatte. Mehrmals haben wir solche myelinisierte Körper auch an unmyelinisierten Ganglienzellen im Zytoplasma der einzigen Satellitenzellschicht gefunden, sodass solche myelinisierten Einschlüsse sich zumindest teilweise auch ohne Abspaltung von einer bestehenden Myelinhülle ausbilden können. Es besteht aspektmässig ein *fliessender Übergang zu den Lysosomen der Ganglienzellperikarya*, welche ebenfalls von myelinartig geschichteten Membranen umgeben sein können.

Teilweise lassen sich die Unregelmässigkeiten der Ganglienzellmyelinscheide dadurch erklären, dass meist mehr als eine Satellitenzelle an ihrem Aufbau beteiligt ist. ROSENBLUTH (74) hat an einer Zelle beschrieben, wie sich die Schichten zweier Satellitenzellen in alternierenden Spiralen um die Ganglienzelle gelegt haben müssen. In einer weitern Arbeit (76) führt der gleiche Autor Beweise dafür an, dass sich an die Umwicklungsperiode im Prozess der Myelinisation ganz allgemein eine zweite Phase anschliessen muss, in welcher die Myelinschichten durch Apposition an Länge und Dicke zunehmen. Im Krötenkleinhirn überschiesst diese zweite Phase oft beträchtlich; grosse Schlingen überschüssigen Myelins legen sich um die Strukturen der Umgebung. ROSENBLUTH nimmt an, dass auch die von WEBSTER und SPIRO (98) beschriebenen Ein- und Ausbuchtungen der Myelinscheiden im N. ischiadicus des



Abb. 19 Der erste an die Ganglienzelle anschliessende Ranvier'sche Schnürring ist asymmetrisch. Gegen die Ganglienzelle zu (rechte Bildseite) beginnen lockere und semikompakt Myelinschichten, gegen die Nervenfaser zu kompakt Myelinschichten (linke Bildseite). Meerschweinchenspiralganglion, 7 Tage nach Knallexposition, Elektronenmikroskop.

Meerschweinchens auf einer solchen Ueberproduktion von Myelin in der zweiten Phase beruhen. Es ist nicht bekannt, welcher Reiz die Bildung überschüssigen Myelins veranlasst. Bei den Spiralganglienzellen wäre es nun denkbar, dass manche Unregelmässigkeiten der Myelinhülle sich durch Ueberproduktion von Myelin während der zweiten Phase erklären lassen. Möglicherweise kommt es auch im Laufe des Lebens zu Aenderungen im Charakter und in der Zahl der Schichten, sodass bestehende Unregelmässigkeiten ausgeglättet oder neue Unregelmässigkeiten geschaffen werden. Es ist auch abzuwägen, ob die verschiedenen Myelintypen blossen Entwicklungsstadien entsprechen, ob also eine Ganglienzelle zuerst von lockerem Myelin umhüllt wird, welches später in semikompaktes und zuletzt in kompaktes Myelin übergeht. Myelinhüllen aller Typen kommen jedoch auch bei erwachsenen Tieren gleichzeitig vor (39, 77), sodass kaum anzunehmen ist, dass alle Zellen notwendigerweise sämtliche Stufen durchlaufen. Die unmyelinierten Zellen des Meerschweinchen sind auch bei älteren Tieren im gleichen Prozentsatz vorhanden wie bei ganz jungen, sodass sie wohl nie in myelinierte Zellen übergehen. Möglicherweise ist es jedoch so, dass die vorwiegend kompakt myelinierten Zellen erwachsener Tiere in ihrer embryologischen Entwicklung ein lockeres und semikompaktes Stadium durchlaufen haben.

Unmyelinierte Ganglienzellen wurden bis jetzt nur bei Goldfischen und beim Meerschweinchen beschrieben. In unserm menschlichen Material fanden wir jedoch sehr häufig Zellen, welche nur von einer oder von 2–3 zytoplasmatischen Schichten der Satellitenzelle umgeben sind sodass wir sie ebenfalls den unmyelinierten Zellen zurechnen möchten. Die Zahl der Schichten ist beim Menschen ganz allgemein viel niedriger als bei den bis jetzt untersuchten Tierarten. Beim Meerschweinchen und beim Kaninchen überwiegen die gemischt lockern bis semikompakten Myelinscheiden, nur bei der Ratte finden sich vereinzelt kompakt umhüllte Zellen

4 *Diskussion und Schlussfolgerungen*

In der Morphologie des normalen Spiralganglions sind vor allem zwei Fragen von aktuellem Interesse auf der einen Seite ist zu untersuchen, ob morphologisch verschiedene Zellpopulationen abgegrenzt werden können, auf der andern Seite stellt sich die Frage nach morphologisch erkennbaren Funktionsstadien ein und der selben Zelle

Die Differenzierung verschiedener Zelltypen könnte als Grundlage dienen für weitere experimentelle Arbeiten über Probleme der Reizleitung der neuronalen Schaltung im Bereich des Corti schen Organs oder der Empfindlichkeit der verschiedenen Populationen auf Lärm oder andere Noxen. Die Abgrenzung verschiedener Funktionsstadien wiederum wäre von Interesse für Arbeiten über die Reaktion der peripheren cochleären Neurone auf physiologische oder pathologische Reize

a *Abgrenzung verschiedener Zelltypen*

Bereits in der lichtmikroskopischen Zeit wurden im Spiralganglion wiederholt verschiedene Zellpopulationen beschrieben (23 102) ohne dass sich eine Einteilung durchsetzte *Als Kriterien für eine Zelltypen Abgrenzung stehen* nach den neuern Arbeiten Zellgrösse Perikaryontyp und Typus der Satellitenzellhülle zur Verfügung Am einfachsten sind auf diese Weise beim Meerschweinchen zwei Zellpopulationen unterscheidbar Rund 10% kleine unmyelinierte filamentöse Zellen stehen 90 grossen, granulären myelinierten Zellen gegenüber Bei den andern bis jetzt untersuchten Tierarten ist es sehr viel schwerer ebenso klare Zelltypen zu erkennen Beim Goldfisch und bei der Ratte sind die filamentösen Ganglienzellen meist von kompakterem Myelin umgeben als die granulären Perikarya Die Grenze ist jedoch weniger scharf als beim Meerschweinchen, bei welchem zudem die umgekehrte Relation besteht zwischen Perikaryon und Myelintyp, eine Tatsache auf die bereits NISHIMURA *et al.* (61) hingewiesen haben. Beim Kaninchen und bei den untersuchten Affen konnten wir weder anhand der Myelinscheide noch anhand der Perikarya sichere Zelltypen unterscheiden. Beim Menschen scheint ein erheblicher Prozentsatz der Zellen nur von einer oder von 2–3 zytoplasmatischen Lagen der Satellitenzelle umgeben zu sein, sodass wir sie den unmyelinierten Zellen zurechnen möchten. Phasenkontrastmikroskopisch lassen sich beim Menschen zudem auch anhand der Zellgrösse zwei Populationen unterscheiden, doch genügte das erst Stunden post

mortem fixierte Material nicht alle drei Kriterien zur Abgrenzung eventueller Zelltypen zu benützen. Aus dieser Uebersicht ergibt sich, dass vorderhand bei den bis jetzt untersuchten Säugern nur das Meerschweinchen auf einfache und sichere Weise zwei Zellpopulationen unterscheiden lässt. Die bei den andern Species beschriebenen Zelltypen sind weniger scharf definierbar und sind zudem den Meerschweinchentypen nicht analog. Die Untersuchung muss jedoch noch auf andere Tierarten ausgedehnt werden, bevor sich etwas Endgültiges über diese Frage sagen lässt.

Die funktionelle Bedeutung verschiedener Zellpopulationen im Spiralganglion lässt sich zur Zeit noch nicht übersehen. Auf die Frage, ob die beiden Zelltypen beim Meerschweinchen den innern respektive den äussern Haarzellen zugeordnet werden könnten, soll weiter unten eingegangen werden. Es muss jedoch schon hier betont werden, dass aufgrund der vergleichenden Morphologie das Meerschweinchen vorderhand als Spezialfall betrachtet werden muss, sodass am Meerschweinchen erhobene Befunde nicht ohne weiteres auf andere Species übertragen werden dürfen.

b. *Funktionsstadien der Ganglienzelle*

Auch die Frage nach morphologisch erkennbaren Funktionsstadien der Spiralganglienzellen soll weiter unten genauer besprochen werden. Bereits hier müssen jedoch die Befunde von Beck und Michler (13) erwähnt werden, welche beim normalen, unbeschallten Meerschweinchen zyklusartig ineinander übergehende Funktionsstadien der Spiralganglienzellen beschrieben haben. Im Ruhestadium enthält das Perikaryon reichlich Nissl-Schollen, die entweder diffus verteilt sind oder sich in gröberer Form der Kern- oder Zellmembran anlegen. Im Uebergang zur Aktionszelle wird das Plasma ärmer an Nissl-Schollen, die restlichen Schollen sammeln sich am einen Zellpol, während der Kern an den andern Zellpol wandert. Der Nucleolus verliert ebenfalls seine zentrale Lage und wandert an die der Zellmitte zugekehrte Seite des Kerns, wobei er sich in eine nucleolare Blase umwandelt, welche sich zur Substanzabgabe ins Zytoplasma eröffnet. Dieses Stadium wird als Aktionszelle bezeichnet. Nachdem die Nucleolarsubstanz ins Zytoplasma entleert ist, füllt sich das Perikaryon langsam wieder mit Nissl-Schollen, der Kern rückt wieder zur Zellmitte, in seinem Zentrum wird die Nucleolarsubstanz wieder aufgebaut. Bei normalen Meerschweinchen fanden die beiden Autoren $^2/_3$ Ruhe- und $^1/_3$ Aktionszellen, nach Beschallung verschob sich das Verhältnis stark zugunsten der Aktionszellen. Elektronenmikroskopische Bilder der verschiedenen Stadien sind bis jetzt nicht bekannt.

Unsere phasenkontrast- und elektronenmikroskopischen Befunde lassen sich nicht direkt vergleichen mit den Bildern, wie sie Beck und Michler lichtmikroskopisch mit Nissl-Färbungen erhalten haben. Aufgrund unseres Material über die Feinstruktur der Spiralganglienzellen normaler Meerschweinchen ergeben sich jedoch einige Ergänzungen. Eine stärkere Exzentrizität des Kerns in Richtung auf einen der Zellpole haben wir nur sehr selten gesehen, viel häufiger nähert er sich den seitlichen Partien der Zellmembran. Auch hat sich in unserm Material keine konstante Relation zwischen Exzentrizität des Kerns und peripherer Lage der Nucleoli ergeben.

Bei den myelinierten Spiralganglienzellen unbeschallter Meerschweinchen sind mehr als die Hälfte der Nucleoli randständig, während bei den unmyelinierten Zellen des Meerschweinchens sowie bei allen Zellen der übrigen untersuchten Tierarten wie auch beim Menschen die zentrale Lage der Nucleoli bei weitem vorherrscht. Die Abhängigkeit der Nucleoluslage von der Species und dem Zelltyp ist eindrücklich; es scheint auch hier das Meerschweinchen eine Ausnahme zu bilden. Eine vakuoläre Umwandlung des Nucleolus haben wir in normalen Meerschweinchen nie gefunden, wohl aber nach Knallexposition und Kanamycinschädigung (siehe weiter unten). Wir möchten deshalb die Frage offen lassen, ob sich bei ungeschädigten Spiralganglienzellen die Substanzabgabe des Nucleolus wirklich als Entleerung einer Nucleolarblase abspielt (58). Als Zeichen eines erhöhten Stoffaustauschs zwischen Kern und Zytoplasma könnte nach ANDRES (5) auch die Wellung der Kernmembran (Oberflächenerhöhung) gedeutet werden. Auch die Feinstruktur der Perikarya mit ihren wechselnden Anhäufungen von Zellorganellen und deren Formänderungen machen es schwer, bei ungeschädigten Spiralganglienzellen in globo von Ruhe- oder Aktionszellen zu sprechen. Erst sicher geschädigte Zellen (siehe weiter unten) zeigen elektronenmikroskopisch Perikaryonveränderungen, welche teilweise mit den von BECK und MICHLER beschriebenen Aktionszellen verglichen werden könnten.

c. *Schlussfolgerungen*

1. Die Untersuchung der verschiedenen Tierarten und besonders auch des Menschen auf morphologisch unterscheidbare Zellpopulationen im Spiralganglion ist noch nicht vollständig. Anhand der Zellgrösse des Perikaryon und des Satellitenzellhüllen-Typs lassen sich zwar bei verschiedenen Species zwei Zelltypen abgrenzen, es sind diese Zelltypen jedoch nicht von einer Tierart auf die andere übertragbar. Nur beim Meerschweinchen sind die Grenzen zwischen den beiden Zellpopulationen genügend scharf. Es lassen sich beim Meerschweinchen 10% kleine filamentöse unmyelinierte Zellen den restlichen 90% grösseren granulären, myelinierten Zellen gegenüberstellen.

   Das Meerschweinchen scheint auch darin eine Ausnahmestellung einzunehmen, dass nur bei den myelinierten Spiralganglienzellen dieser Tierart die Nucleoli in einem grossen Prozentsatz randständig angeordnet sind. Bei den unmyelinierten Meerschweinchenzellen und bei allen andern bis jetzt untersuchten Tierarten wie auch beim Menschen überwiegen die zentral gelegenen Nucleoli bei weitem.
2. Die Abgrenzung von Funktionsstadien normaler Spiralganglienzellen bereitet bei feinstruktureller Untersuchung grosse Schwierigkeiten. Es gelingt an ungeschädigten Ganglienzellen nicht, die Zellen in globo als Ruhe- oder als Aktionszellen zu bezeichnen.
3. Die mannigfachen Einschlusskörper der Spiralganglienzellen sind so polymorph, dass bis jetzt kein befriedigendes Einteilungsschema vorliegt. Ihre Zahl und Grösse ist in unserm Material grossen individuellen Schwankungen unterworfen. Herkunft, Entwicklung und funktionelle Bedeutung der einzelnen Einschlüsse sind noch weitgehend hypothetisch.

Die osmiophilen Pigmentgranula nehmen beim Menschen mit dem Alter an Grösse und Zahl zu. Grosse myelinierte Einschlüsse kommen auch bei unmyelinierten Zellen im Zytoplasma der Satellitenzellen vor sie können deshalb zumindest teilweise auch ohne Abspaltung von einer bestehenden Myelinhülle auftreten.
4 Im Verlauf der Hörbahn stellt die Strecke von der Habenula perforata bis zum N acusticus eine Summe gegeneinander isolierter Reizleitungskanäle dar da weder an den myelinierten Dendriten, noch an den Ganglienzellen, noch an den Axonen irgendwelche Synapsen untereinander oder mit den efferenten oder mit unmyelinierten autonomen Nervenfasern beobachtet wurden.

III PATHOLOGIE DES SPIRALGANGLIONS

A Kurze Literaturübersicht

Bereits in den ältern Standardwerken ist eine Fülle von Material über die Pathologie des Spiralganglions bei Spontanerkrankungen und nach experimentellen Läsionen zusammengefasst In neuerer Zeit hat WITTMAACK (101) die Ergebnisse seiner frühern Arbeiten in einer grössern Monographie zusammengestellt und gesichtet Die neueste Uebersichtsdarstellung stammt von ALTMANN (3) sie ist jedoch noch vor den Arbeiten der letzten Jahre entstanden und berücksichtigt deshalb noch keine elektronenmikroskopischen Befunde Aus diesen Uebersichten ergibt sich dass sich die Beobachtungen in der Pathologie der peripheren akustischen Neurone oft widersprechen In manchen Fragen stehen sich seit Jahrzehnten festgefahrene Meinungen diametral gegenüber und auch die in den letzten Jahren erschienenen Arbeiten haben an dieser Situation wenig geändert Aus verschiedenen Gründen hat sich das Interesse in der Pathologie der ersten Neurone der Hörbahn immer mehr auf die degenerativen Veränderungen konzentriert Wir können uns deshalb darauf beschränken, im Lichte der neuern Literatur auf die degenerativen Erkrankungen genauer einzugehen während wir für die Missbildungen und die entzündlichen Erkrankungen auf die erwähnten Uebersichten verweisen können

Unabhängig von der Ursache (physikalische chemische vaskuläre oder auch entzündlich bedingte Degeneration) werden in der Literatur drei Formen der Degeneration der peripheren cochleären Neurone unterschieden Bei der *primären Degeneration* werden die Neurone von der auslösenden Noxe direkt betroffen, bei der *sekundären Degeneration* schädigt die Noxe die Haarzellen des Corti'schen Organs, und erst deren Ausfall führt zu einer sekundären absteigenden Degeneration (ALTMANN) der zugehörigen Neurone Als dritte Form wird die *retrograde Degeneration* abgegrenzt wie sie auftritt nach direkter Läsion der Dendriten oder Axone der Spiralganglienzellen, sei es experimentell oder zum Beispiel durch den Druck eines Acusticusneurinoms. Wir möchten auf die im Einzelfall oft umstrittene Zuordnung der spontan oder experimentell entstandenen Degenerationsbilder zur einen oder andern dieser Gruppen weiter unten eingehen es muss aber bereits hier erwähnt werden dass die theoretisch wie praktisch wohl interessanteste Form der sekundären absteigenden Degeneration von ALTMANN (3) selbst stark bezweifelt wird Er nimmt vielmehr an, das Corti'sche Organ und die ersten Neurone der Hörbahn seien weitgehend unabhängig voneinander Bei den bald nach der Geburt ertaubenden Dalmatinerhunden zum Beispiel komme es zu ausgedehnten Degenerationen im Corti'schen Organ ohne dass das Spiralganglion sekundär degeneriere Wenn es zu korrespondierenden Ausfällen in beiden Strukturen komme so habe die

auslösende Noxe gleichzeitig sowohl das Endorgan wie die ersten Neurone geschädigt eine gegenseitige Beeinflussung im Sinne einer sekundären ab- oder aufsteigenden Degeneration sei in keinem Fall zwingend bewiesen worden.

Als weitere Vorbemerkung muss noch auf die methodischen Schwierigkeiten hin gewiesen werden, welche sich bei Arbeiten auf diesem Gebiet ergeben. Wie bei der Beurteilung des Corti'schen Organs ist es infolge der schwer zugänglichen Lage des Spiralganglions nicht leicht tatsächliche von postmortalen Veränderungen zu unterscheiden. ECKERT MÖBIUS (21) und FERNÁNDEZ (77) haben die postmortalen *Veränderungen der Spiralganglienzellen und bei der Verarbeitung entstehende Arte* fakte eingehend beschrieben. Noch schwerer ist es, elektronenmikroskopisch beginnende Autolyse oder Verarbeitungsartefakte von tatsächlichen degenerativen Veränderungen auseinanderzuhalten. Die meisten Arbeiten über die Degeneration der peripheren cochleären Neurone beruhen auf der Analyse von Schnitten oder Schnittserien. Schnitte erlauben aber in der vergleichenden Beurteilung der Ausfälle im Corti'schen Organ und im Spiralganglion nur bedingt zuverlässige Aussagen, besonders wenn das Material vorher entkalkt werden musste. Endlich sei auch noch erwähnt, dass ein Vergleich der morphologischen Befunde mit vorausgegangenen Funktionsprüfungen vorderhand nur beim Menschen mit der wünschenswerten Genauigkeit vorgenommen werden kann. Versuchstiere können zwar besser fixiert und verarbeitet werden, doch lassen sich deren Hörstörungen mit den existierenden Methoden noch nicht mit der notwendigen Sicherheit und Genauigkeit messen. Ein Hinweis auf diese Schwierigkeiten ist unumgänglich denn wenn die Befunde der verschiedenen Autoren so oft divergieren, liegt das nicht allein an der Komplexität der Verhältnisse an sich es hat zudem jeder Autor noch mit den Unvollkommenheiten seiner Methoden zu kämpfen.

1 *Die Schallschädigung der peripheren cochleären Neurone*

Seit WITTMAACK 1907 (100) erstmals Veränderungen im Spiralganglion nach experimenteller Schallexposition beschrieb ist die Literatur über die schallbedingte Degeneration der peripheren cochleären Neurone in kaum mehr überschbarem Masse angewachsen. Wir möchten zuerst eine Gruppe von Arbeiten ausscheiden, welche sich nicht mit den irreversiblen Ausfällen der peripheren Neurone nach hohen Schalldosen befassen, sondern die grösstenteils noch reversiblen, unmittelbaren Reaktionen der Spiralganglienzellen auf Schallreize beschreiben. Vor allem mit biochemischen Methoden wurde versucht solche reversible Sofortreaktionen zu erfassen. Die Arbeit von HAMBERGER und HYDÉN (36) wirkte dabei stimulierend durch die versuchsweise angewandte, neuartige Methodik. Sie fanden wie einige der spätern Autoren (87 90 50) eine Abnahme der Ribonucleinsäuren im Zytoplasma der Ganglienzellen, die sich einige Zeit nach der Schallexposition wieder normalisierte Die mit verfeinerter Methodik durchgeführte Wiederholung der Experimente von HAMBERGER und HYDÉN durch HALLÉN *et al* (35) ergab jedoch trotz höherer Schalldosis keine signifikanten Unterschiede mehr zwischen beschallten und Kon

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A. Kurze Literaturübersicht

Bereits in den ältern Standardwerken ist eine Fülle von Material über die Pathologie des Spiralganglions bei Spontanerkrankungen und nach experimentellen Läsionen zusammengefasst. In neuerer Zeit hat WITTMAACK (101) die Ergebnisse seiner frühern Arbeiten in einer grössern Monographie zusammengestellt und gesichtet. Die neueste Uebersichtsdarstellung stammt von ALTMANN (3); sie ist jedoch noch vor den Arbeiten der letzten Jahre entstanden und berücksichtigt deshalb noch keine elektronenmikroskopischen Befunde. Aus diesen Uebersichten ergibt sich, dass sich die Beobachtungen in der Pathologie der peripheren akustischen Neurone oft widersprechen. In manchen Fragen stehen sich seit Jahrzehnten festgefahrene Meinungen diametral gegenüber, und auch die in den letzten Jahren erschienenen Arbeiten haben an dieser Situation wenig geändert. Aus verschiedenen Gründen hat sich das Interesse in der Pathologie der ersten Neurone der Hörbahn immer mehr auf die degenerativen Veränderungen konzentriert. Wir können uns deshalb darauf beschränken, im Lichte der neuern Literatur auf die degenerativen Erkrankungen genauer einzugehen, während wir für die Missbildungen und die entzündlichen Erkrankungen auf die erwähnten Uebersichten verweisen können.

Unabhängig von der Ursache (physikalische, chemische, vaskuläre oder auch entzündlich bedingte Degeneration) werden in der Literatur drei Formen der Degeneration der peripheren cochleären Neurone unterschieden. Bei der *primären Degeneration* werden die Neurone von der auslösenden Noxe direkt betroffen, bei der *sekundären Degeneration* schädigt die Noxe die Haarzellen des Corti'schen Organs, und erst deren Ausfall führt zu einer „sekundären absteigenden Degeneration" (ALTMANN) der zugehörigen Neurone. Als dritte Form wird die *retrograde Degeneration* abgegrenzt, wie sie auftritt nach direkter Läsion der Dendriten oder Axone der Spiralganglienzellen, sei es experimentell oder zum Beispiel durch den Druck eines Acusticusneurinoms. Wir möchten auf die im Einzelfall oft umstrittene Zuordnung der spontan oder experimentell entstandenen Degenerationsbilder zur einen oder andern dieser Gruppen weiter unten eingehen; es muss aber bereits hier erwähnt werden, dass die theoretisch wie praktisch wohl interessanteste Form der sekundären absteigenden Degeneration von ALTMANN (3) selbst stark bezweifelt wird. Er nimmt vielmehr an, das Corti'sche Organ und die ersten Neurone der Hörbahn seien weitgehend unabhängig voneinander. Bei den bald nach der Geburt ertaubenden Dalmatinerhunden zum Beispiel komme es zu ausgedehnten Degenerationen im Corti'schen Organ, ohne dass das Spiralganglion sekundär degeneriere. Wenn es zu korrespondierenden Ausfällen in beiden Strukturen komme, so habe die

HOSSLI (41) wies darauf hin, dass die äussern Haarzellen empfindlicher sind als die innern; in seinem Material degenerierten die Zellen des Spiralganglions aber erst dann, wenn auch die innern Haarzellen ausgefallen waren. Es degenerieren immer viel weniger Ganglienzellen, als man nach der Zahl der ausgefallenen Haarzellen erwarten möchte (84). Das Spiralganglion kann völlig normal aussehen in einem Bereich, wo sämtliche Haarzellen des Corti'schen Organs verloren gingen. SCHUKNECHT (84) nimmt an, der Ganglienzellausfall gehe vielmehr parallel zum Ausfall der Stützzellen des Corti'schen Organs, besonders der Pfeilerzellen. Auch SANDO (81) kommt aufgrund seiner Experimente zu ähnlichen Schlüssen. SCHUKNECHT (84) hat auch beobachtet, dass Ganglienzellen nach dem Untergang des gesamten Corti'schen Organs zwar ihre Dendriten verlieren, selbst aber in einem pathologischen Zustand überleben können. Von besonderem Interesse sind die spärlichen Angaben über den zeitlichen Ablauf der Degeneration. Bereits HOSSLI (41) stellte fest, die Degeneration der peripheren Neurone hinke zeitlich hinter den Ausfällen im Corti'schen Organ nach, und LURIE *et al.* (55) fanden bei Meerschweinchen erst 9 Tage nach der Schallexposition degenerierende Nervenfasern und erst nach 3–4 Wochen einen Ausfall an Ganglienzellen.

Aufgrund der Literatur kommt es somit nach Schallexposition zuerst zu einer reversiblen, sofort nach der Schallbelastung einsetzenden Reaktion der Spiralganglienzellen, die bei höhern Schalldosen übergehen kann in die erst später einsetzende irreversible Degeneration der peripheren Neurone. Ein Teil der Spiralganglienzellen scheint sich jedoch auch bei vollständig zerstörtem Corti'schem Organ wieder zu erholen und zu überleben. Die Frage, ob ein reiner Haarzellausfall genügt, um die Degeneration entsprechender Neurone auszulösen, oder ob die Neurone ebenfalls direkt vom Schall geschädigt werden, wird in der Literatur verschieden beantwortet.

— *Die Degeneration der peripheren cochleären Neurone nach Verabreichung ototoxischer Substanzen*

Wie bei der Schallexposition stellt sich auch nach Verabreichung ototoxischer Substanzen die Frage, ob die beobachteten Degenerationsausfälle der peripheren Neurone als reine absteigende Degeneration nach entsprechenden Haarzellausfällen im Corti'schen Organ zu betrachten seien, oder ob die ototoxische Substanz gleichzeitig sowohl die Haarzellen wie auch die Zellen des Spiralganglions schädige. Aus der umfangreichen Literatur über die [illegible] Streptomyces-Antibiotica (Übersicht bei KONONEN (48)) geht hervor, dass zumindest lokalisatorisch die Neuronenausfälle den Haarzellausfällen einigermassen parallelgehen (Ka[illegible] *et al.*). Jedoch auch Angaben, dass die Ausfälle im Spiralganglion diejenigen des Corti'schen Organs übertreffen können (63, 71), ja dass sich die Degeneration sogar auch auf die cochleären cerebralen Kerne erstrecken kann (51, 71). [illegible] *et al.* (10[illegible]) wiesen nach, dass Kanamycin nach parenteraler Applikation in der [illegible] Resorptionsphase in den Innenohrflüssigkeiten zwar [illegible] Werte des Serum erreicht

dass es jedoch aus den Innenohrflüssigkeiten viel langsamer verschwindet als aus dem Blut oder aus Organen wie Gehirn, Leber oder Herz. Kanamycin wird also über eine beträchtliche Zeitspanne in den Innenohrflüssigkeiten retiniert, sodass das Spiralganglion ohne weiteres durch Diffusion eine erhebliche Menge aufnehmen könnte. Dementsprechend hat MÜSEBECK (60) in den Spiralganglienzellen nach Applikation von Dihydrostreptomycin eine viel stärkere Abnahme des Sulfhydrylgehalts gemessen als zum Beispiel in den Haarzellen des Corti'schen Organs. An andern ototoxischen Substanzen wurden Spiralgangliendegenerationen nach Chinin (80, 101) und nach Arsacetin (23) beschrieben.

Die Morphologie der degenerativen Veränderungen in den Zellen des Spiralganglions wurde elektronenmikroskopisch bisher erst von AWATAGUCHI *et al.* (9) und von FRIEDMANN *et al.* (30) beschrieben. Die japanischen Autoren fanden nach Streptomycin und Kanamycin in den Spiralganglienzellen des Meerschweinchens die gleichen Degenerationszeichen wie nach Schallexposition. Wiederum waren die unmyelinierten Zellen stärker verändert als die myelinierten. FRIEDMANN *et al.* beobachteten nach Neomycin neben Veränderungen der Mitochondrien und der Nissl-Schollen vor allem das Auftreten von multizystischen Cytosomen und von Myelinfiguren.

3. *Die Degeneration der Spiralganglienzellen nach Läsion der Axone oder Dendriten*

Dass die experimentelle Durchtrennung der Axone im Bereich des Nervenstammes des N. acusticus zu einer praktisch vollständigen Degeneration der Spiralganglienzellen führt, ist seit langem bekannt. Dagegen ist es technisch sehr viel schwieriger, die Dendriten in der kurzen Strecke zwischen Spiralganglion und Corti'schem Organ zu durchschneiden. Immerhin wird aufgrund von Experimenten mit mechanischer Zerstörung des Corti'schen Organs angenommen, dass die Spiralganglienzellen nicht nur auf Läsionen ihrer Axone, sondern auch der Dendriten ausserordentlich empfindlich sind (81, 84). Bei den Spinalganglien zum Beispiel führen entsprechende Läsionen der Axone und Dendriten nur in einem gewissen Prozentsatz zur retrograden Degeneration des Ganglienzellkörpers, und bei den vestibulären peripheren Neuronen ist es überhaupt nicht möglich, durch experimentelle Durchschneidung des Nervenstammes eine retrograde Degeneration der Ganglienzellen zu erreichen. Neuere Untersuchungen (80) haben allerdings die Einschränkung ergeben, dass nach Durchtrennung des N. acusticus zwar die Zellen des Spiralganglions und die myelinierten Dendriten in der Lamina spiralis ossea regelmässig degenerieren, die unmyelinierten Dendritenabschnitte und die afferenten Nervenendigungen jedoch erhalten bleiben. Die retrograde Degeneration macht gewissermassen im Bereich der Habenula perforata Halt. Es wird deshalb angenommen, die unmyelinierten Dendritenabschnitte seien in Bezug auf ihre Ernährung nicht mehr von den Spiralganglienzellen abhängig. Irgendwelche Regenerationsversuche sind weder an den Spiralganglienzellen noch an deren Achsenzylindern jemals nach

gewiesen worden (84). Im Gegensatz zu andern Sinnesorganen bleibt auch das Endorgan, also die Haarzellen des Corti'schen Organs, trotz vollständigem Ausfall seiner Neurone immer intakt. Die theoretisch denkbare „sekundäre aufsteigende Degeneration" (ALTMANN) wurde somit nie beobachtet.

4. *Die Altersdegeneration des Spiralganglions*

Dass die Zahl der Spiralganglienzellen sich mit zunehmendem Alter stark verringert, wurde bereits von GUILD *et al.* (34) quantitativ bewiesen. Entsprechende Befunde ergaben sich auch bei alten Versuchstieren (18). Da in höherm Alter aber immer auch gleichzeitig degenerative Ausfälle im Corti'schen Organ zu finden sind, wurde wiederholt versucht, die quantitative Relation der Ausfälle in den beiden Strukturen zu bestimmen. Die Ergebnisse wurden verschieden interpretiert; es ist deshalb die alte Streitfrage bis heute nicht entschieden, ob es eine reine primäre Altersdegeneration der peripheren cochleären Neurone gibt, oder ob es sich vorwiegend um eine sekundäre absteigende Degeneration nach primärem Haarzellausfall handle. Die Abklärung der Frage wird zudem noch dadurch kompliziert, dass es wohl eine Presbyacusis im Sinne einer reinen Altersatrophie gar nicht gibt, sondern dass es sich dabei um den Summationseffekt verschiedener krankhafter Prozesse (vor allem vaskulärer Natur) handelt. SAXÉN und v. FIEANDT (82) und auch ALTMANN (3) nehmen zwar an, die „senile Atrophie des Ganglion spirale" sei in einem Teil der Fälle die einzige Ursache der Presbyacusis, weil nur sie regelmässig auf die basalen Teile der Cochlea beschränkt sei, während die Ausfälle im Corti'schen Organ entweder viel geringer oder dann aber regellos über die Windungen verteilt seien. Von dieser rein ganglionären Form der Presbyacusis trennen die erwähnten Autoren eine vaskuläre (angiosklerotische) Form ab. In den letzten Jahren wird die pathologische Anatomie der Presbyacusis noch differenzierter behandelt. SCHUKNECHT (86) unterscheidet vier Formen (eine sensorische Form mit atrophischen Veränderungen vor allem im Corti'schen Organ, eine neurale Form mit vorwiegendem Verlust von Neuronen der Hörbahn, eine metabolische Form mit Veränderungen vorwiegend in der Stria vascularis sowie eine mechanische Form mit Veränderungen der schwingenden Strukturen des Ductus cochlearis) und HANSEN *et al.* (38) deren fünf (Ausfälle im Endorgan, Ausfälle an peripheren Neuronen, vorwiegend vaskuläre Schäden, Ausfälle im Nervenstamm, Ausfälle in den höhern akustischen Bahnen und Zentren). Im Zusammenhang mit den Fortschritten der klinischen Audiologie werden so in zunehmendem Mass Veränderungen in den höhern Abschnitten der Hörbahn zur Erklärung der Presbyacusis herangezogen. Von audiologischer Seite wurde die ganglionäre Natur der Presbyacusis vor allem von LANGENBECK (52) unterstützt, indem er audiometrisch einen der Presbyacusis gleichzusetzenden Ganglienzelltyp vom Haarzelltyp der Innenohrschwerhörigkeit unterscheiden konnte. An einem ausgedehnten menschlichen Material versucht BREDBERG (14), mit seiner neuen Methodik der Lösung der Frage näherzukommen.

B Eigene Degenerationsversuche

Wir stellten uns für unsre eigenen Versuche die Aufgabe das morphologische Bild der Spiralgangliendegeneration zu studieren wie es sich nach dem Ausfall des Endorgans darbietet Um dabei die Ausfälle im Ganglion mit denen des Corti schen Organs vergleichen zu können, wurde eine kombinierte Methodik mit Häutchenpräparaten des Corti schen Organs (22) und Schnittuntersuchung der korrespondierenden Spiralganglionabschnitte gewählt Es erschien für unsre Absicht günstig begrenzte aber eindeutige Ausfälle im Corti'schen Organ zu erzielen welche mit erhaltenen Partien verglichen werden konnten Zur experimentellen Schädigung des Corti'schen Organs verwendeten wir Knallexposition (Startpistolenschüsse) und ein ototoxisches Antibioticum (Kanamycin) Eine Beurteilung des zeitlichen Ablaufs der Degeneration war nur möglich wenn die Schädigung als einmalige Dosis verabreicht werden konnte Dies bedingte eine hohe Schall resp Kanamycindosi für Kanamycin kam zudem nur die direkte Applikation ins Mittelohr in Frage da sonst mit einer einmaligen Dosis keine sichern Haarzellau falle hervorgerufen werden können Wir wählten Meerschweinchen als Versuchstiere nicht nur aus Gründen der methodischen Einfachheit sondern vor allem deswegen, weil sich beim Meerschweinchen auf einfache und sichere Weise zwei Zellpopulationen im Spiralganglion unterscheiden lassen Am Spezialfall des Meerschweinchens konnte so die Frage studiert werden ob morphologisch unterscheidbare Ganglienzelltypen sich auch verschieden verhalten auf die beiden angewendeten Noxen Wir hofften zudem wenigstens stellenweise eine selektive Zerstörung der äussern Haarzellen zu erhalten da nach einem solchen selektiven Ausfall aus dem Bild der Degeneration im Spiralganglion sich möglicherweise Rückschlüsse auf die normale Organisation der peripheren Neurone in Bezug auf die beiden Rezeptortypen (innere und äussere Haarzellen) ziehen lassen

1 *Material und Methoden*

Verwendet wurden 18 Meerschweinchen aus verschiedenen Zuchtstämmen im Alter von wenigen Wochen. Tiere ohne einwandfreien Ohrmuschelreflex nach *Preyer* wurden ausgeschieden. Die eine Hälfte der Tiere wurde innert 2–3 Stunden 100–200 mal aus einer Distanz von 10–20 cm dem Knall blinder Startpistolenschüsse ausgesetzt Die andere Hälfte der Tiere erhielt in Barbituratnarkose beidseits eine einmalige Dosis von Kanamycin (etwa 0 1 ml einer 60 %igen wässrigen Lösung von Kanamycinsulfat) durch das Trommelfell ins Mittelohr gespritzt. In verschiedenen Zeitabständen nach Knallexposition resp Kanamycininjektion wurden die Tiere durch Dekapitation getötet, die Bullae eröffnet die knöcherne Schale der Cochleae samt der Stria vascularis unter 1,5 %iger veronalgepufferter Lösung von Osmium tetroxyd entfernt und der Modiolus im Bereich seines spiraligen Gefässkanals mehrfach perforiert. Nach 2 stündiger Osmiumfixation im Eiskasten und Auswaschen der Präparate in Ringer Lösung wurden vom Corti schen Organ ½ 1½ 2½ und 3¼ Windungen von der Basis entfernt sektorenförmige Häutchenpräparate



Abb. 11. Corti'sches Organ (Häutchenpräparat) Meerschweinchen, 3 Tage nach Knallexposition, $1\frac{1}{2}$ Windungen von Basis. Randgebiet der selektiven Zerstörung der äussern Haarzellen. IHC = innere Haarzellen alle intakt, P = Pfeilerzellen, 1 = erste, 2 = zweite, 3 = dritte Reihe der äuss. Haarzellen. Fels = erhaltene äuss. Haarzellen. Phasenkontrast mikroskop 1500 ×

entnommen (genaues Vorgehen siehe ENGSTRÖM *et al.* (22)), wobei darauf geachtet wurde, dass die peripheren Teile der Nervenfasern in der Lamina spiralis ossea mit erfasst wurden. Den Häutchenpräparaten genau entsprechende Sektoren des Modiolus mit dem Spiralganglion wurden herausgebrochen, ohne Entkalkung dehydriert und in Epoxyreain eingebettet. Mit einem LKB-Ultrotom wurden 0,5–2μ dicke radiäre Querschnitte des Spiralganglions angefertigt, mit Paraphenylendiamin (24) kontrastiert und im Phasenkontrastmikroskop beurteilt.

Anhand der Häutchenpräparate (Abb. 11, 22) wurden für die Haarzellen des Corti'schen Organs Cochleogramme aufgenommen (genaues Vorgehen siehe ENGSTRÖM *et al.* (22)), welche lückenlos den Zustand jeder einzelnen Haarzelle im untersuchten Sektor festhalten. Für die vergleichende Untersuchung mit dem Spiral-



Abb. 12. Häutchenpräparat des Corti'schen Organs 28 Tage nach Knallexposition (100 Schüsse). 1 ½ Windungen von der Basis. Randgebiet des Zerstörungsmaximums, Narbenlinie mit spinnenartigen Ausläufern. Rechts sind zwei innere Haarzellen und einige Pfeilerzellen erhalten (Pfeil). Phasenkontrastmikroskop 60 ×

ganglion waren vor allem jene Sektoren geeignet, welche über eine genügend lange Strecke hin (dh. rund 100 innern Haarzellen entsprechend) einen gleichförmigen Haarzellbefund aufwiesen. Eine graduelle Zu- oder Abnahme der Haarzellausfälle vom einen Ende des Sektors zum andern hätte die sichere Korrespondenz zu den Ausfällen im Spiralganglion gefährdet, es wurde deshalb in solchen Fällen auf eine vergleichende Beurteilung verzichtet. Anhand der Häutchenpräparate liess sich auch ein Nervenfaserausfall in der Lamina spiralis ossea ohne Schwierigkeiten erkennen, sobald er ein gewisses Mass überschritt (Abb. 14). Obwohl es die Methode nicht erlaubte, den Prozentsatz der ausgefallenen Nervenfasern genau anzugeben, genügte es für die anvisierte Fragestellung durchaus, feststellen zu können, ob die Mehrzahl der Nervenfasern erhalten oder ausgefallen war. Auch die Beurteilung der Degeneration im Spiralganglion kommt naturgemäss nicht an die Exaktheit der Cochleogramme heran. Immerhin erlaubte es die Methode, jede im Schnitt getroffene Ganglienzelle einzeln zu beurteilen und sowohl die relative Zahl der pathologisch veränderten Zellen wie auch den Schweregrad der Schädigung zur Klassifizierung zu benützen. Da der Prozentsatz der geschädigten Zellen dem Schweregrad der Schädigung im allgemeinen parallelging, wurde darauf verzichtet, die

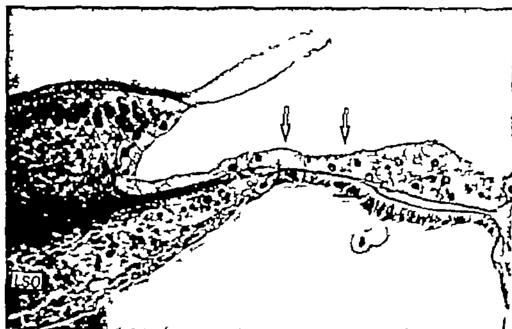


Abb. 11. Corti'sches Organ (Pfeile) 42 Tage nach Knallexposition (160 Schüsse), 2 Windungen von der Basis (Bereich des Zerstörungsmaximums). Vollständiger Faserschwund in der Lamina spiralis ossea (LSO). Phasenkontrastmikroskop 310

beiden Beurteilungsgesichtspunkte zu trennen. Als schwer bezeichneten wir die Degeneration im Spiralganglion, wenn rund ein Drittel oder mehr der Ganglienzellen ausgeprägte degenerative Veränderungen aufwies oder sogar in Auflösung begriffen war; als mittlere Degeneration, wenn weniger als rund ein Drittel der Ganglienzellen solche Veränderungen aufwies; und als fragliche bis geringe Degeneration, wenn nur vereinzelte Ganglienzellen irreversibel geschädigt erschienen.

Von den 9 Tieren, welche Schüssen ausgesetzt wurden, konnten 14 Cochleae ausgewertet werden. 4 Cochleae wiesen *keine Haarzellausfälle auf*, wobei mindestens zweimal eine unbemerkte Mittelohrentzündung als verläufender Schallschutz gewirkt haben dürfte. Von den 9 Kanamycintieren konnten 10 Cochleae von 7 Tieren ausgewertet werden. 5 Cochleae zeigten neben entzündlichen Veränderungen im Mittelohr auch eine ausgeprägte Labyrinthitis; es sollen diese Labyrinthitisfälle anhangsweise weiter unten besprochen werden. 3 Cochleae zeigten keine Haarzellausfälle und fielen deshalb für eine vergleichende Beurteilung ausser Betracht.

— *Ergebnisse*

a. *Degeneration nach Knallexposition* (Tab. 1)

Mit der angewendeten hohen Zahl von Startpistolenschüssen erzielten wir im Corti'schen Organ schwere Ausfälle, welche sich mit grosser Regelmässigkeit auf die

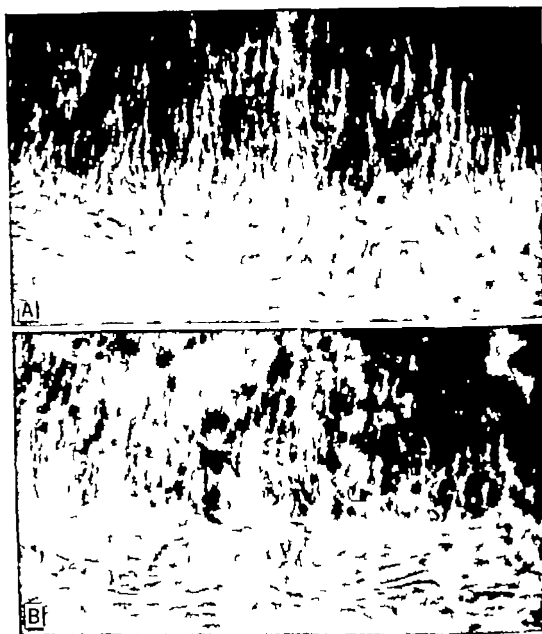


Abb. 14.) Normales Nervenfaserbild der Lamina spiralis ossea, b) Zerfall der Nervenfasern 3 Tage nach Knallexposition (*00 Schuss) Hä t hnpräparate 1½ Windungen von der Basis. Phasenkontrastmikroskop 80 ×



Abb. 15. Spiralganglion 30 Tage nach Knallexposition (200 Schüsse), 1 ½ Windungen von der Basis. Corti'sches Organ im entsprechenden Bereich vollständig zerstört. Ganglienzellzahl und Nervenfasern stark reduziert, efferente Bündel (EB) jedoch intakt. Phasenkontrastmikroskop 780

zweite Windung konzentrierten. Nur bei der Cochlea Nr. 14 verschob sich das Wirkungsmaximum aus unbekannten Gründen apicalwärts in die untere Hälfte der dritten Windung. Die Lokalisation des Wirkungsmaximum entsprach also den Befunden, wie sie beim Meerschweinchen immer wieder beschrieben wurden. Bereits 3 Tage nach der Knallexposition waren im Bereich des Zerstörungsmaximums sämtliche äussern und innern Haarzellen verschwunden, auch die Stützzellen waren in diesem Bereich bereits nach 3 Tagen vollständig kollabiert. Nur anhand einer einfachen oder doppeltkonturierten Narbenlinie mit stellenweisen spinnenartigen Ausläufern konnte in den Häutchenpräparaten das zerstörte Corti'sche

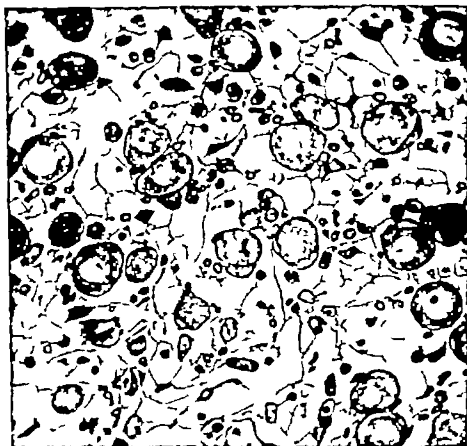


Abb 16 Spiralganglion 42 Tage nach Knallexposition (160 Schüsse), 2 Windungen von der Basis. Reduktion der Ganglienzellzahl auf rund die Hälft Phasenkontrastmikroskop 80×

Organ noch lokalisiert werden (Abb 1.) Im Schnitt zeigte sich diese Narbenlinie *als flacher Trümmerhügel*, welcher sich über der sonst bereits von einem *durch* gehenden kubischen Epithel bedeckten Basilarmembran erhebt (Abb 13) In den Randgebieten wird die Narbenlinie von Inseln unterbrochen, welche Gruppen von teilweise stark dislozierten Pfeilerzellköpfen entsprechen. In den vom Wirkungsmaximum weiter entfernten Partien (½ und 2½ Windungen von der Basis) fand sich nur noch ein partieller oder vollständiger Kollaps der äussern Haarzellen bei erhaltenen innern Haarzellen. Die Spitzenregion war nie betroffen. Das Ausmass der Haarzellausfälle war bereits 3 Tage nach der Knallexposition voll ausgebildet und blieb während der ganzen Beobachtungsperiode konstant Die Nervenfasern in der Lamina spiralis ossea waren bereits 3 Tage nach der Knallexposition im Bereich des Wirkungsmaximums in vollem Zerfall begriffen (Abb 14) Es waren zu diesem Zeitpunkt neben Myelinbruchstücken auch bereits Körnchenzellen zu sehen, während in den spätern Stadien solche Makrophagen und Myelinbruchstücke fehlen. Der abgeschlossene Nervenfaserzerfall lasst sich dann nur noch an einer zahlenmässigen

Reduktion der Fasern erkennen. Im Spiralganglion konnten wir erst nach 10–20 Tagen sichere Zelluntergänge finden, die Ganglienzellen zeigten jedoch in jenen Abschnitten, welche dem Wirkungsmaximum entsprachen, bereits 3–7 Tage nach der Knallexposition deutliche Strukturveränderungen. Während der Beobachtungsperiode (längstens 42 Tage) kam es nirgends zu einem Ausfall von mehr als rund der Hälfte der Ganglienzellen (Abb 16) auch nicht in jenen Abschnitten, welche einem vollständig zerstörten Corti'schen Organ entsprachen. Mehrmals waren über lange Strecken hin sämtliche äussern Haarzellen selektiv ausgefallen, während die innern Haarzellen auch bei sorgfältiger Beurteilung aller optischen Schichten keine pathologischen Veränderungen erkennen liessen. An diesen Stellen war im allgemeinen weder im Spiralganglion noch im Bereich der Lamina spiralis ossea eine merkliche Degeneration von Ganglienzellen resp. Nervenfasern zu sehen, wobei natürlich vereinzelte Zell- oder Nervenfaseruntergänge mit unserer Methodik nicht sicher erfasst werden konnten. Dreimal beobachteten wir aber bei der gleichen Konstellation im Corti'schen Organ, also bei anscheinend intakten innern Haarzellen, einen massiven Zerfall von Nervenfasern in der Lamina spiralis ossea. Das zahlenmässige Verhältnis von myelinierten und unmyelinierten Spiralganglienzellen blieb unverändert, unabhängig davon, ob im Corti'schen Organ bloss sämtliche äussern oder sowohl die äussern wie die innern Haarzellen ausgefallen waren. Auch bei stärkster zahlenmässiger Reduktion der Ganglienzellen bei vollständiger Zerstörung des Corti'schen Organs nahm der Prozentsatz der unmyelinierten Zellen nicht merkbar ab. Das efferente intraganglionäre Spiralbündel blieb regelmässig intakt (Abb 15).

b *Degeneration nach Kanamycin* (Tab 2)

Obwohl das ototoxische Antibioticum nicht parenteral, sondern direkt ins Mittelohr eingebracht wurde, folgten die Haarzellausfälle im Corti'schen Organ ausnahmslos dem bereits bekannten Muster (48). Bei geringer Ausdehnung beschränkten sich die Ausfälle auf die äussern Haarzellen der untern Basalwindung, bei stärkerer Schädigung breiteten sich die Ausfälle an den äussern Haarzellen apicalwärts aus, während sich gleichzeitig von der Spitze aus basalwärts fortschreitende Ausfälle an innern Haarzellen dazugesellten. Erst bei noch stärkerer Schädigung fallen auch basal die innern Haarzellen aus, die äussern Haarzellen waren in diesem Stadium meist schon durchgehend bis zur Spitze kollabiert. Trotz einmaliger Dosis nahmen die Ausfälle an Haarzellen über Wochen stetig zu. Nach 4 Worten waren regelmässig sämtliche äussern Haarzellen kollabiert, nach 2 Monaten waren in allen Windungen sämtliche Sinneszellen ausgefallen. In diesem Endstadium verschwanden auch an einigen wenigen Stellen die Pfeilerzellen. Im Spiralganglion nahmen die Degenerationsausfälle ebenfalls im Laufe der Wochen stetig zu, sicher irreversibel geschädigte Ganglienzellen waren wie nach der Knallexposition erst 10–20 Tage nach der Kanamycininjektion zu sehen. Der Schwund an Ganglienzellen ging jedoch nicht parallel zu den Ausfällen an Haarzellen im Corti'schen Organ. Die schwersten Degenerationsbilder konzentrierten sich immer mehr gegen die Spitze zu. An mehreren Stellen

Tabell 1 Knallexponiert Meerschweinchen.

Cochlea-Bezeichnung	Ueberlebenszeit	[illegible]			1½			1			3½		
		Haarzellen	Fasern	Ganglion	Haarzellen	Fasern	Ganglion	Haarzellen	Fasern	Ganglion	Haarzellen	Fasern	Ganglion
83 R	3	O ×	O	O	× ×	+++	O	O O	O	O	O O	O	O
83 L	3	O 50	O	O	× ×	+++	O	O ×	+++	O	O O	O	O
85 R	3	O O	O	O	O ×	+++ O	O	O O	O	O	O O	O	O
85 L	3	O 40%	O	O	× ×	+++	O	O ×	++	O	O O	O	O
7 R	7	O O	O	O	× ×	++	O	O ×	O	+	O O	O	O
7 L		O ×	O	O	× ×	++	+		?			?	
84 R	7	O O	O	O	×	+++	O		?		O O	O	O
86 R	10	O ×	O	O	× ×	+++	++	O O	O	O		?	
86 L	10	O ×	O	O	× ×	+++	++	O O	O	O		?	
73 R	14	O ×	O	O	×	++	++	O ×	O	+	O O	O	O
74 R	28	O ×	O	O	× ×	+++	++	O ×	O	+	O O	O	O
74 L	28	O 70	O	O	O ×	O	O	O O	O	O	O O	O	O
87 R	30	O ×	O	O	× ×	+++	+++	O 50	O	O	O O	O	O
75 R	42	O 70	O	+	O O	O	O	×	+++	+++		?	

Tabelle Meerschweinchen nach intratympanaler Kanamycininjektion.

	Cochlea-Bezeichnung	Überlebenszeit	½			1½						3		
			Haarzellen	Fasern	Ganglion	Haarzellen	Fasern	Ganglion	Haarzellen	Fasern	Ganglion	Haarzellen	Fasern	Ganglion
1	57 L		O ×	O	O	O ×	O	O	O O	O	O	O O	O	O
	55 R	7	O ×	O	O	O O	O	O	O O	O	O	O O	O	O
3	55 L	7	O ×	O	O	O O	O	O	O O	O	O	O O	O	O
4	63 R	18	O ×	O	++	O O	O	+	O O	O	O	O O	O	+
5	63 L	18	O ×	O	+	O ×	O	+	O O	O	O	50*	O	+++
6	63 R	28	× ×	O	+++	×	+	++		++	+++	×	++	++
7	67 R	35	O ×	O	+	40* ×	O	++	[illegible] ×	O	+++	×	+	+++
8	68 R	60	× ×	+++	+++	×	+	+++	× ×	++	+++		++	+++
9	68 L	60	× ×	O	++	×	++	++	×	++	+++	×	+++	+++
0	69 R	98	× ×	++	++	×	++	+++		++	+++		?	

Erklärungen zu den Tabellen 1 und 2.

In der Tabelle 1 sind die Cochleae Nr. 2, 4, 8, 9 und 13 jeweils 200 Schummen ausgesetzt worden, die übrigen 160 [illegible]. ½–3½ = Windungen von der Basis. Ü = Überlebenszeit in Tagen. In den Kolonnen „Haarzellen" entsprechen die obern Signaturen den innern, die untern den äussern Haarzellen. O = 90–100% der Haarzellen intakt, × = 90–100% der Haarzellen ausgefallen, in den übrigen Fällen ist der Prozentsatz der erhaltenen Haarzellen angegeben. In den Kolonnen „Fasern" bedeutet O = kein Faserausfall in der Lamina spiralis ossea, + = geringer, ++ = mittlerer, +++ = schwerer Faserausfall. In den Kolonnen „Ganglion" bedeutet O = keine sicheren Degenerationszeichen, + = fragliche bis geringe Degeneration, ++ = mittlere, +++ = schwere Degeneration.

ergab sich auch der Eindruck, die Spiralganglienzellen degenerierten zeitlich vor den entsprechenden Dendriten in der Lamina spiralis ossea, eventuell sogar vor den korrespondierenden Haarzellen. Im Vergleich zu den knallexponierten Tieren kam es nach Kanamycin zu einer stärkeren Reduktion der Ganglienzellzahl. Nach Knallexposition leerte sich der Ganglionquerschnitt nie so stark, nicht einmal im Bereich des Wirkungsmaximums. Auch nach Kanamycin kam es oft über lange Strecken hin zu einem selektiven Ausfall sämtlicher äussern Haarzellen. In den entsprechenden Abschnitten des Spiralganglions und in der Lamina spiralis ossea waren dann viel weniger Zell- und Nervenfaserverluste festzustellen als dort, wo sowohl die äussern wie die innern Haarzellen zugrunde gegangen waren. Ein selektiver Ausfall der innern Haarzellen konnte nirgends erzielt werden. Einmal waren in der Spitzenwindung alle innern Haarzellen kollabiert bei einem Ausfall von 50% der äussern Haarzellen; im korrespondierenden Spiralganglionsektor fanden wir eine quantitativ und qualitativ schwere Degeneration. Wie bei den knallexponierten Tieren nahm auch nach Kanamycin der Prozentsatz der unmyelinierten Zellen nicht ab, auch wenn sich das Ganglion stark gelichtet hatte. Der Prozentsatz blieb sich auch gleich, wenn selektiv sämtliche äussern Haarzellen kollabiert waren.

c. *Die Morphologie der degenerierenden Ganglienzellen*

Das Bild der Degeneration der Spiralganglienzellen war bei den knallexponierten und den Kanamycin-geschädigten Tieren so ähnlich, dass sich eine gesonderte Besprechung erübrigt.

Im Frühstadium der Schädigung fanden wir sowohl phasenkontrast- wie elektronenmikroskopisch deutlich geschwollene Ganglienzellkerne. Die Kerne verlagerten sich oft an die Zellperipherie, und zwar weitaus häufiger in die seitlichen Partien als gegen einen der Zellpole zu. Der Nucleolarapparat wird grösser und sitzt oft breitbasig der Kernmembran auf, ohne dass wir allerdings von einer signifikanten Zunahme der randständigen Nucleoli sprechen könnten, da auch im normalen Meerschweinchenspiralganglion rund die Hälfte der Nucleoli peripher gelegen sind. Bei elektronenmikroskopischer Kontrolle ergibt sich, dass die Vergrösserung des Nucleolarapparates vor allem durch den vergrösserten und aufgelockerten Nucleolarsatelliten bedingt ist, während der Nucleolus selbst weder in seiner Grösse noch in seiner Struktur merklich verändert erschien. In den Perikarya der Ganglienzellen sind *bereits* wenige Tage nach Knallexposition oder Kanamycininjektion phasenkontrastmikroskopisch bedeutende Veränderungen zu sehen. Die als homogene graue Schollen in normalen Zellen verteilte Nissl-Substanz scheint zu grossen, strukturlosen Flächen zusammenzufliessen, welche vor allem die Zellpole ausfüllen, hie und da aber auch den Kern als Mantel umgeben (Abb. 17–23). Elektronenmikroskopisch zeigen diese homogenen Flächen ein ribosomenreiches endoplasmatisches Reticulum. Hie und da finden sich auffallende Wirbelbildungen des endoplasmatischen Spaltensystems. Der homogene Aspekt solcher Zonen hat seinen Grund darin, dass sie weitgehend frei sind von Mitochondrien, Golgi-Feldern und Einschlusskörpern (Abb. 24). Es



Abb. 17 Spiralganglion 10 Tage nach Knallexposition (200 Schüsse), 1½ Windungen von der Basis. Degenerierende Ganglienzellen (schwarzer Pfeil) und Nervenfasern (weisser Pfeil). Phasenkontrastmikroskop 1540×

sammeln sich diese Zellorganellen vor allem in Nähe des Kerns, weshalb diese Gebiete bereits im Phasenkontrastmikroskop vermehrt granuliert erscheinen. Die Ganglienzellmitochondrien sind wenig verändert. Golgi-Zonen finden sich recht häufig an der Aussenseite der Kernmembran, wo sich ein Nucleolus an deren Innenseite angelegt hat (Abb. 25). Die Satellitenzellhülle zeigt in diesem Stadium nur diskrete Veränderungen. Der Satellitenzellkern ist ebenfalls geschwollen, die an und für sich schon grossen, elektronendichten Mitochondrien der Satellitenzelle nehmen an Grösse zu. Die Myelinhülle ist in ihrer Schichtung noch vollkommen intakt, legt sich aber besonders im Bereich der Zellpole vermehrt in Falten. Die Nervenfasern selbst sind hie und da leicht geschwollen, im übrigen aber noch ohne wesentliche Veränderungen.

In spätern Stadien der Degeneration verliert der geschwollene Kern seine pralle runde Form. Er ist dann im Schnitt unregelmässig eingebuchtet, ohne dass es jedoch

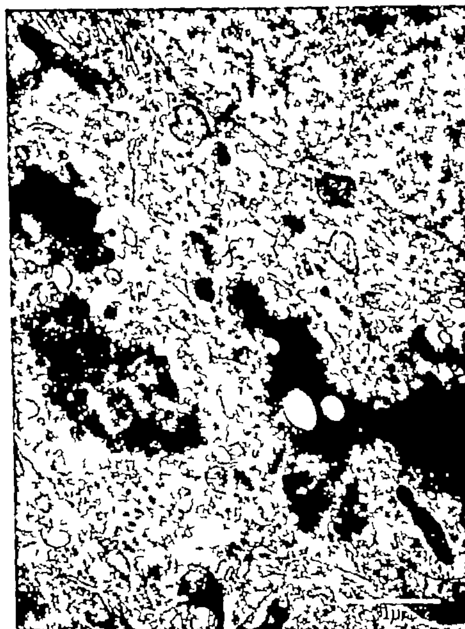


Abb. 18. Myelinisierte Spiralganglienzelle. Meerschweinchen 3 Tage nach Knallexposition (160 Schüsse). Teilweise vakuolisiert Pigmentkörper, welche von multiplen kleinern Tröpfchen umgeben sind. Die kleinern Tröpfchen weisen eine dreischichtige Membran auf; die Membran der Pigmentkörper ist bloss ein- oder zweischichtig. Elektronenmikroskop.

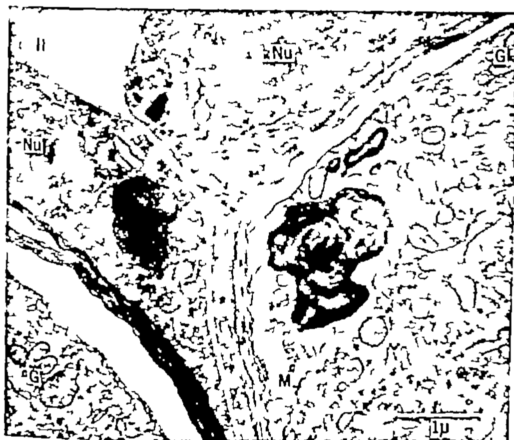


Abb. 19. Myelinisierte Spiralganglienzellen, Meerschweinchen 7 Tage nach Knallexposition (100 Schüsse). I = Interzellulärraum, Zytoplasmatische Schicht der Satellitenzelle mit grossen Golgi Zonen und einem Riesenmitochondrium. Die innerst zytoplasmatische Schicht der Satellitenzelle um die Ganglienzelle rechts (M) weist einen grossen myelinisierten Einschlusskörper auf. Elektronenmikroskop.

zu einer eigentlichen Kernpyknose käme. Im vergrösserten Nucleolarsatelliten treten kleinere oder grössere vakuolenartige Aufhellungen auf, und zwar sowohl bei zentral gelegenen wie auch bei den randständigen Nucleoli. Die Struktur des Karyoplasmas bleibt auch in stark geschädigten Zellen gut erhalten. Die Perikarya sind immer noch auffallend reich an Ribosomen, die homogen erscheinenden Zonen haben sich ausgedehnt. Mitochondrien und Golgi Zonen sind immer noch in Kernnähe konzentriert. Die verschiedenen Einschlusskörper nehmen langsam an Zahl und Grösse zu, auch die Wirbelbildungen und ähnliche Formationen der endoplasmatischen Spalten werden ausgeprägter. Die Myelinhüllenfalten verstärken sich so, dass im Schnitt oft nicht zu entscheiden ist, ob bereits eine echte Abschnürung von Myelinkugeln vorliegt (Abb. 19, 27). Die Faserabgänge schwellen an, die Nervenfasern zeigen teilweise ebenfalls eine starke Schwellung, teilweise scheinen sie zusammen



Abb 20 Spiralganglion Meerschweinchen, 7 Tage nach Knallexposition (100 Schüsse). Spiralganglienzelle (links) mit weitgehend zerstörter Myelinscheide (Myelinbruchstück rechts) M = Mitochondrium mit Vakuolen, E = Einschluss mit myelinartig geschichteter Membran, enthält ein Pigmentkörperchen.

zudintern, wobei sie sich in starke Windungen legen. Die Mitochondrien der Satellitenzellen wachsen sich nun zu eigentlichen Riesenmitochondrien mit unregelmässigen Cristae aus (Abb 21) die zytoplasmatische Hülle der unmyelinierten Zellen wird vakuolisiert (Abb 28 29)

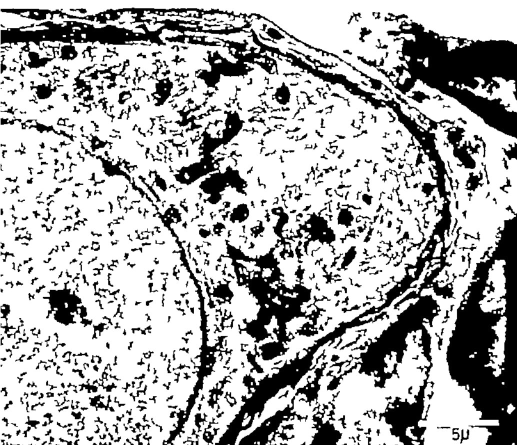
Die endgültige Auflösung der Ganglienzelle scheint an den Faserabgängen zu beginnen, wo sich die Myelinhülle in Kugeln abzuspalten beginnt wobei aber die ursprüngliche Schichtung weiter beibehalten wird. Die Bruchstücke der Myelinhülle und der Ganglienzelle selbst werden von Makrophagen aufgenommen, deren Herkunft nicht angegeben werden kann. Hie und da hatten wir den Eindruck, auch die Satellitenzellen könnten phagozytieren. Wir können anhand unseres Material auch nicht entscheiden ob die im immer leerer werdenden Gesichtsfeld übrigbleibenden Kerne ursprünglich den Satellitenzellen zugehörten oder ob es sich um Bindege-



Abb. 21 Myelinierte Spiralganglienzelle, Meerschweinchen, 7 Tage nach Knallexposition (160 Schüsse). Riesenmitochondrium (RM) im Zytoplasma der Satellitenzelle (SC). M = Myelinschichten, G = Perikaryon der Ganglienzelle

webskerne handelt. Wenn die Makrophagen verschwunden sind, bleibt ein lockeres Bindegewebe zurück, in welches die überlebenden, unauffällig erscheinenden Ganglienzellen und einige erhaltene Nervenfasern eingestreut sind. Das efferente intraganglionäre Spiralbündel ist auch bei elektronenmikroskopischer Kontrolle völlig intakt.

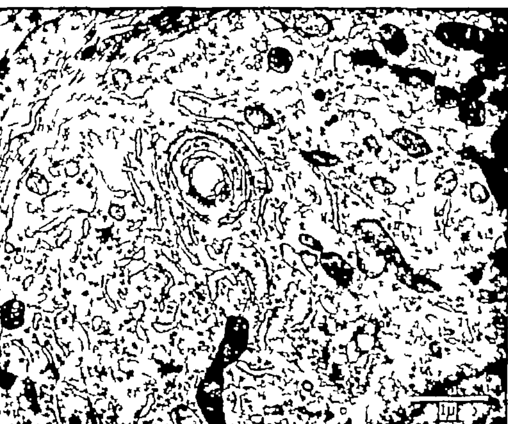
Zusammenfassend lässt sich sagen, dass bei elektronenmikroskopischer Untersuchung sich die ersten Veränderungen im Bereich des Nucleolarapparates und des endoplasmatischen Reticulums finden. Der Nucleolarsatellit wird grösser und enthält Vakuolen, das ribosomenreiche endoplasmatische Reticulum sammelt sich zu



bb. 21 Myelinisierte Spiralganglienzelle, Meerschweinchen 28 Tage nach Kanamycininjektion, pikale Windung. Das endoplasmatische Reticulum sammelt sich gegen den Zellpol, während sich Mitochondrien und Golgi-Zonen eher dem Kern nähern.



Abb. 2 Myelinisierte Spiralganglienzelle [illegible] Windung. Randständiger Kern [illegible] heterochromatin. Auf der [illegible] Nucleolarapparat gegenüber [illegible]



26 Myelinisierte Spiralganglienzelle, Meerschweinchen 28 Tage nach Kanamycininjektion, ...ale Windung Konzentrisch angeordnete Spaltmembranen des endoplasmatischen Reticulums. Beginn von Sequestration im Zentrum?


SC
M
G

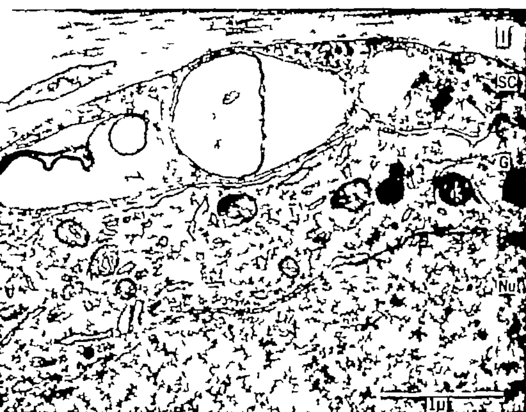


Abb. 21 Unmyelinisierte Spiralganglienzelle Meerschweinchen 28 Tage nach Kanamycininjektion, apicale Windung. Vakuolisierung der einzigen zytoplasmatischen Schicht der Satellitenzelle (SC)
I = Interzellularraum, G = Perikaryon der Ganglienzelle
N = Nucleus der Ganglienzelle.



Abb. 29 Spiralganglion Meerschweinchen, 20 Tage nach Kanamycininjektion, basale Windung. Oben unmyelinisierte Ganglienzelle (G), deren einzige Satellitenzellschicht (SC) in der rechten Bildhälfte grosse Vakuolen aufweist. Unten links Teil einer myelinisierten Ganglienzelle mit myelinisiertem Einschlusskörper in einer der Satellitenzellschichten. I = Interstitieller Raum, N = Nervenfaser mit pathologisch aufgelockerter Myelinscheide?



Abb 34 Spiralganglion Meerschweinchen, 28 Tage nach Kanamycininjektion, apicale Windung. Hälfte eines Ranvier'schen Schnürrings. Die Strukturen der Myelinschichten sind noch recht gut erhalten, während der Achsenzylinder bereits weitgehende degenerative Veränderungen aufweist (Pfeile): kleinvakuoliger Zerfall, Pigmentkörper, polymorphe Einschlusskörper

Organ war in allen Windungen vollständig zerstört der Limbus und die Basilarmembran jedoch gut erhalten. Die Basilarmembran bedeckte ein einschichtiges kubisches oder plattes Epithel Die Scalae und auch der nur teilweise noch abgrenzbare Ductus cochlearis waren von lockerem Bindegewebe mit weiten Gefässräumen ausgefüllt, gegen den Apex zu fand sich in zunehmendem Mass auch neugebildeter Knorpel und Knochen. Zwischen den Blättern der Lamina spiralis ossea fehlten die Nervenfasern ganz, im Spiralganglion waren im apicalen Bereich sämtliche Ganglienzellen verschwunden, gegen die Basis zu blieben jedoch vereinzelte Zellen erhalten Der N acusticus war in vollem Zerfall begriffen Makrophagen fanden sich aber auch im ehemaligen Spiralganglion und in der Lamina spiralis ossea Auch die Limbusepithelien waren oft prall gefüllt mit eosinophilen Granula wobei wir nicht entscheiden können, ob es sich um resorbiertes oder um in den Epithelzellen selbst entstandenes Material handelt. Im Unterschied zur Degeneration nach Knallexposition oder auch zu den Kanamycinschäden ohne Labyrinthitis war hier das intraganglionäre Spiralbündel regelmässig schwer reduziert meist sogar völlig verschwunden. Die Blutgefässe zeigten keine merklichen Veränderungen.

3 *Diskussion und Schlussfolgerungen*

a. *Unterschiede zwischen Kanamycin und knallbedingter Degeneration*

Aus unserm Material ergeben sich in mehreren Punkten prinzipielle Unterschiede zwischen dem Kanamycin- und dem knallbedingten Degenerationsbild der peripheren cochleären Neurone Nach Knallexposition folgte einem totalen Ausfall des Corti schen Organs die Degeneration der Mehrzahl de korrespondierenden Neurone, selektiver Ausfall der äussern Haarzellen dagegen führte nur zum Ausfall einer geringen Neuronenzahl (auf die Ausnahmen von dieser Regel soll weiter unten eingegangen werden) Im zeitlichen Ablauf degenerierten nach Knallexposition die Nervenfasern in der Lamina spiralis ossea vor den entsprechenden Spiralganglienzellen, und erst zuletzt erreichte die Degeneration die Nervenfasern des N acusticus im Modiolus. Nach intratympanal verabreichtem Kanamycin dagegen schienen die Ganglienzellen oft zeitlich vor den entsprechenden Nervenfasern in der Lamina spiralis ossea Degenerationszeichen aufzuweisen, die Degeneration im Spiralganglion war oft stärker als dem Ausfall an Haarzellen entsprochen hätte Die schwersten Ausfälle konzentrierten sich nach Kanamycin immer mehr gegen die Spitze zu Obwohl im Bereich des Wirkungsmaximums das Corti sche Organ samt seinen Stützzellen nach Knallexposition viel stärker zerstört war als nach Kanamycin, kam es doch nach Kanamycin zu einer viel stärkeren Reduktion der Ganglienzellzahl als nach Knallexposition. Nach der einmaligen Kanamycindosis nahmen die Ausfälle im Corti schen Organ und im Spiralganglion über Wochen stetig zu während nach Knallexposition die bereits nach drei Tagen voll ausgebildeten Ausfälle im Corti schen Organ sich im spätern Verlauf nicht mehr weiter ausdehnten und auch im Spiralganglion der Degenerationsprozess nach etwa 4 Wochen abgeschlossen schien Diese Langzeitwirkung von intratympanal verabreicht m Kanamycin ent pricht

der langen Verweildauer in den Innenohrflüssigkeiten (99) Wie OLIVIERI und ROSSI (63) für Neomycin festgestellt haben ist das Ausmass der Haarzell und Spiral ganglienzellausfälle auch nach Kanamycin nicht nur dosisabhängig sondern auch abhängig von der seit der Applikation verstrichenen Zeit Die Langzeitwirkung von Kanamycin erklärt jedoch das abweichende Bild der Degeneration der ersten Neurone nicht vollständig Es drängt sich vielmehr die von verschiedenen Autoren bereits vorgebrachte Vermutung auf Kanamycin wirke nicht nur auf die Haarzellen des Corti'schen Organs, sondern gleichzeitig auch auf die Zellen des Spiralganglions toxisch. Wir möchten eine solche direkte Schädigung der Ganglienzellen mindestens bei der intratympanalen Applikation von Kanamycin annehmen. Ob sie auch für parenteral verabreichtes Kanamycin gilt können wir nicht entscheiden. Es muss aber in Betracht gezogen werden dass zusätzlich zu einer direkten toxischen Wirkung auf die Spiralganglienzellen auch noch retrograde Degenerationsprozesse im Sinne der sekundären absteigenden Degeneration sich abspielen sodass es sich in Wirklichkeit um eine gemischte Degeneration handeln könnte Weshalb es in unsern Fällen zu den schwersten Degenerationsbildern ausschliesslich im Spitzenbereich kam, könnte einmal seinen Grund darin haben, dass die innern Haarzellen nach Kanamycin im Spitzenbereich zuerst ausfallen, und dass möglicherweise im Spitzenbereich besonders viele der peripheren Neurone den innern Haarzellen zugeordnet wären Es könnte auch sein, dass der Anteil der langen Spironeurone von Windung zu Windung verschieden ist Denkbar wäre auch dass die Spiralganglienzellen im Spitzenbereich durch Diffusion aus den Innenohrflüssigkeiten mehr Kanamycin aufnehmen als weiter basal weil die knöchernen Trennwände im Spitzenbereich doch deutlich dünner sind als in den basalen Windungen Ein vaskulärer Faktor ist wenig wahrscheinlich, da die Gefässe in unsern Fällen nirgends merklich verändert erschienen. Es muss in diesem Zusammenhang erwähnt werden dass auch in jenen Cochleae welche auf die Kanamycininjektion mit einer Labyrinthitis reagierten, der Prozentsatz der überlebenden Ganglienzellen gegen die Basis stetig zunahm. Auch hier also konzentrierten sich die schwersten Ausfälle an Ganglienzellen gegen die Spitze zu Das histologische Bild der Labyrinthitis nach intratympanal verabreichtem Kanamycin entspricht der Beschreibung wie sie WITTMAACK (101) von der serösen Labyrinthitis gab Es kommt in den Innenohrräumen zwar zu ausgedehnten Fibrosierungen mit teilweiser Knochenneubildung doch bleibt trotz vollständiger Zerstörung des Corti schen Organs die Basilarmembran und auch der Limbus erhalten. WITTMAACK konnte solche seröse Labyrinthitiden experimentell auslösen, wenn er verschiedene Substanzen ins Mittelohr einbrachte Es könnte sich demnach auch im Falle von Kanamycin vorwiegend um eine unspezifische chemische Labyrinthitis handeln, welche die spezifischen Wirkungen des Kanamycins in diesen Fällen weitgehend überdeckt

Das morphologische Bild der verschiedenen Stadien des Zelluntergangs zeigte keine merklichen Unterschiede zwischen kanamycingeschädigten und knallexponierten Tieren, der Zerfall der Ganglienzellen spielte sich auf gleiche Weise ab Auch die myelinierten Dendriten und die Axone der Spiralganglienzellen zeigten in beiden

Fällen dieselben Zerfallsbilder, nur dass der Zerfall der Nervenfasern in der Lamina spiralis ossea nach Kanamycin teilweise hinter der Ganglienzelldegeneration nachhinkte.

Wegen der Langzeitwirkung und der wahrscheinlichen direkten toxischen Wirkung auf die Ganglienzellen lassen sich die Kanamycinbefunde nicht für differenziertere Auswertungen verwenden, die Zahl der beteiligten Faktoren ist zu gross. Es kann nur soviel gesagt werden, dass die unmyelinierten Ganglienzellen beim Meerschweinchen in unserm Material nicht in einem höhern Prozentsatz degenierten als die myelinierten. Nach unsern Befunden sind sie demnach nicht empfindlicher auf Kanamycin als die myelinierten, während Awataguchi *et al.* (9) in ihrem Material elektronenmikroskopisch bei den unmyelinierten Zellen viel ausgeprägtere Veränderungen fanden.

b. *Vergleich der Spiralganglienzelldegeneration mit der primären Reizung bei den Zellen der Spinalganglien*

Wenn in unserm Material nach Knallexposition die Degeneration von den Haarzellen des Corti'schen Organs aus zeitlich gestaffelt zuerst die myelinierten Dendriten in der Lamina spiralis ossea, dann die Spiralganglienzellen und zuletzt die Nervenfasern des N. acusticus im Modiolus erreichte, so entspricht dies dem Ablauf einer retrograden Degeneration nach Durchtrennung der Dendriten. Es war deshalb zu untersuchen, ob auch die degenerativen Veränderungen der Spiralganglienzellen im Bild der primären Reizung eine Entsprechung fänden, wie sie in den Spinalganglienzellen nach Läsionen der Axone oder Dendriten auftritt. Die primäre Reizung ist an Spinalganglien in neuerer Zeit vor allem von Cervós-Navarro (16, 17) und von Andres (6) untersucht worden. Nach Cervós-Navarro kommt es bei der primären Reizung zur Kernschwellung, der Kern verlagert sich in die Zellperipherie, der Nucleolus wird grösser und dichter und rückt zur Kernmembran, das endoplasmatische Reticulum mit seiner auffallend ribosomenreich gewordenen Matrix wandert vom Kern weg in die Randpartie der Zelle, während Mitochondrien, Golgi-Zonen und Pigmentgranula sich eher in Nähe des Kerns ansammeln. Cervós-Navarro bezeichnet alle diese Vorgänge als aktive reparative Zellveränderungen, es sei deshalb die Bezeichnung primäre Reizung dem Begriff der retrograden Degeneration vorzuziehen. Andres unterteilt das Bild der primären Reizung nach dem Schweregrad der Veränderungen in verschiedene Chromatolyse-Stadien, wobei das schwerste Stadium ("toxische Chromatolyse") nicht mehr als reaktiv, sondern bereits als regressiv bezeichnet wird. Ein Vergleich zeigt, dass auch die degenerierenden Spiralganglienzellen ein Stadium durchlaufen, welches der primären Reizung gleicht. Der Kern schwillt ebenfalls an, er wandert allerdings nicht so regelmässig zur Zellperipherie wie bei der primären Reizung. Gleichartig sind bis zu einem gewissen Grad auch die Veränderungen des Nucleolapparates. Auch die Veränderungen in den Perikarya entsprechen sich, das ribosomenreich gewordene endoplasmatische Reticulum sammelt sich auch in geschädigten Spiralganglienzellen in grossen

peripheren Zonen, während sich Mitochondrien und Golgi Zonen eher dem Kern nähern Das gleiche dürfte auch für die osmiophilen Pigmentgranula gelten, welche sich in degenerierenden Spiralganglienzellen auffallend häufig zu rosettenartigen Gruppen in der Zellmitte zusammenfinden. Wenn man annimmt dass die primäre Reizung als reparative Reaktion der Zelle noch nichts aussagt über deren weiteres Schicksal, dass also die primäre Reizung sowohl zur Restitutio ad integrum wie zum Zelluntergang führen kann, so können dementsprechend die bis jetzt beschriebenden Veränderungen auch in den Zellen des Spiralganglions noch reversibel sein. Für den beginnenden Zelluntergang dürften erst die Veränderungen der Myelinscheide typisch sein. Sie finden sich gehäuft im Bereich der Faserabgänge wo schon bei Normaltieren oft Unregelmässigkeiten der Myelinschichten vorkommen. Es ist deshalb einleuchtend dass solche präexistente Unregelmässigkeiten als Locus minoris resistentiae bei der Degeneration am leichtesten zur Abspaltung von Myelinkugeln Anlass geben

Wie bei der primären Reizung stellt sich auch bei degenerierenden Spiralganglienzellen die Frage welche Faktoren im Einzelfall bestimmen, ob sich eine Zelle erholen wird, oder nicht Möglicherweise wird diese Frage in der Zelle selbst entschieden, je nachdem die reparativen oder die regressiven Vorgänge die Oberhand gewinnen. Als zusätzlicher Unsicherheitsfaktor muss aber in Betracht gezogen werden, dass die überlebenden Zellen ganz oder teilweise solchen Haarzellen zugeordnet sein könnten, welche ausserhalb der Schädigungszone gelegen sind. Bei den überlebenden Spiralganglienzellen könnte es sich demnach um Neurone handeln, welche als Spironeurone doch noch Kontakt haben könnten mit weiter entfernten intakten Haarzellen. In unserm Material sehen die überlebenden Ganglienzellen unauffällig aus es finden sich auch immer eine gewisse Zahl überlebender Nervenfasern, sodass wir nicht sagen können, ob es wirklich dendritenlose überlebende Ganglienzellen gibt, wie sie von SCHUKNECHT (84) beschrieben wurden.

c *Degeneration nach selektivem Ausfall der äussern Haarzellen*

Sowohl nach Kanamycin wie nach Knallexposition kam es häufig über lange Strecken hin zu einem selektiven Ausfall sämtlicher äussern Haarzellen, sodass mit Sicherheit Abschnitte des Spiralganglions untersucht werden konnten, welche dieser Konstellation im Corti'schen Organ entsprachen. Da SPOENDLIN (88) weitaus die Mehrzahl der peripheren cochleären Neurone den innern Haarzellen zuordnet wäre zu erwarten, dass in solchen Fällen der Ausfall an Nervenfasern und Ganglienzellen kaum erkennbar bleiben müsste Mehrheitlich entsprachen unsre Befunde dieser Erwartung Wir fanden aber dreimal nach Knallexposition einen massiven Nervenfaserausfall direkt anschliessend an offensichtlich intakte innere Haarzellen. Zweimal fanden wir einen solchen diskrepanten Befund in der dritten Windung einmal in der zweiten, nie jedoch in der Basalwindung Es wäre deshalb denkbar dass ein von Windung zu Windung verschieden grosser Anteil an Spironeuronen für die Diskrepanz verantwortlich wäre Es wäre auch abzuwägen, ob die Nervenfasern

in der Lamina spiralis ossea eventuell direkt mechanisch vom Knall geschädigt werden. Im Bereich mechanischer Belastungsspitzen könnte dann der Ausfall an Nervenfasern unabhängig sein von der Konstellation der Haarzellausfälle Möglicherweise wurden an den Stellen mit diskrepantem Befund auch bloss die unmyelinierten Dendriten mechanisch geschädigt was wir mit unserer Methode nicht kontrollieren konnten. Der Zustand der Stützzellen kann kaum für die Diskrepanz verantwortlich sein, da in allen Fällen der Stützapparat des Corti'schen Organs erhalten blieb Leider ist es bis jetzt kaum möglich, selektiv die innern Haarzellen auszuschalten. Es fehlt also das Gegenexperiment welches vielleicht besser Aufschluss geben könnte

d *Die Zuordnung der myelinierten Ganglienzellen*

Die auch im Phasenkontrastmikroskop leicht erkennbaren kleinen unmyelinierten Spiralganglienzellen des Meerschweinchens machen bei Normaltieren in allen Windungen rund 10 der Zellen aus. Wenn man der Vermutung zustimmt dass die Mehrzahl der peripheren Neurone den innern Haarzellen zugeordnet sei so wäre es zahlenmässig durchaus möglich, dass die unmyelinierten Ganglienzellen den äussern Haarzellen entsprächen. Der Prozentsatz an unmyelinierten Zellen blieb jedoch sowohl nach Kanamycin wie nach Knallexposition im Rahmen der auch bei Normaltieren vorkommenden Schwankungsbreite unverändert Er sank auch nicht ab, wenn selektiv sämtliche äussern Haarzellen ausgefallen waren, oder wenn die Degeneration die Ganglienzellzahl erheblich reduziert hatte Unsere Befund machen es deshalb wenig wahrscheinlich dass die unmyelinierten Spiralganglienzellen des Meerschweinchens selektiv den äussern Haarzellen entsprechen. Da sie weder auf Kanamycin noch auf Knallexposition in einem höhern Prozentsatz degenerieren als die myelinierten Zellen, scheinen sie auch nicht empfindlicher zu sein auf die beiden Noxen. Es muss aber nochmals betont werden, dass die Befunde nicht ohne weiteres vom Meerschweinchen auf andere Tierarten übertragen werden dürfen da die bis jetzt beschriebenen Zelltypen bei den verschiedenen Species untereinander nicht sicher vergleicher sind.

e. *Die für die Degeneration der peripheren Neurone verantwortlichen Faktoren*

Wenn selbst ganz einfach angelegte Degenerationsversuche zu so uneinheitlichen Ergebnissen führen, dass für fast alle Einzelbefund mehrere Erklärungsmöglichkeiten offen bleiben, so ist es leicht einzusehen, dass auch auf die grundsätzliche Frage nach dem degenerationsauslösenden Faktor keine Antwort gegeben werden kann. Die Degenerationsbefunde nach intratympanal verabreichten Kanamycin können wir weitgehend verstehen, wenn wir eine doppelte toxische Wirkung sowohl auf die Haarzellen des Corti'schen Organs wie auf die Spiralganglienzellen annehmen. Ungelöst bleibt vor allem, weshalb sich die schwersten Ausfälle an Ganglienzellen im Spitzenbereich konzentrierten Nach Knallexposition dagegen erscheint der Ausfall an peripheren Neuronen viel eher al sekundäre Degeneration nach dem Ausfall der entsprechenden Abschnitte des Corti'schen Organs. Dabei können wir nicht

entscheiden, ob ein reiner Haarzellkollaps genügt um die Degeneration der entsprechenden Neurone auszulösen oder ob eventuell durch den Knall die Nervenendigungen oder die unmyelinierten Dendriten geschädigt werden müssen damit es zur retrograden Degeneration der peripheren afferenten Neurone kommt Soweit wir anhand der Häutchenpräparate feststellen konnten ist der Zustand der Stützzellen nicht allein verantwortlich für die Auslösung der Neuronendegeneration. Wir fanden immer wieder Stellen mit offensichtlich intaktem Stützapparat und starkem Ausfall an korrespondierenden Neuronen Manche Befunddiskrepanz liesse sich wohl erklären wenn man über die Verteilung von Ortho- und Spironeuronen in den verschiedenen Windungen besser orientert wäre

f *Schlussfolgerungen*

1 Sowohl mit Knallexposition wie mit intratympanal verabreichtem Kanamycin liessen sich Ausfälle sowohl im Corti schen Organ wie auch an peripheren cochleären Neuronen erzielen. Die Degeneration der Neurone zeigte sowohl im zeitlichen Ablauf wie auch in der örtlichen Verteilung und dem Schweregrad deutliche Unterschiede zwischen den knallexponierten und den Kanamycin Tieren Diese Unterschiede stützen die Annahme Kanamycin wirke zumindest bei intratympanaler Applikation nicht nur auf die Haarzellen des Corti'schen Organs, sondern auch direkt auf die Spiralganglienzellen toxisch Die durch Kanamycin hervorgerufenen Ausfälle sind sowohl im Corti schen Organ wie im Spiralganglion abhängig von der Dosis aber auch abhängig von der Zeit die seit der Applikation verstrichen ist

2. Nach Knallexposition dagegen folgte die Degeneration der peripheren Neurone weitgehend dem Ablauf einer retrograden Degeneration indem zuerst die Nervenfasern in der Lamina spiralis ossea dann die Spiralganglienzellen und erst zuletzt die Nervenfasern des N acusticus im Modiolus von der Degeneration erreicht wurden Auch bei vollständigen Ausfall des Corti schen Organs mitsamt seinen Stützzellen kam es bis zum Ende der Beobachtungsperiode nie zum Ausfall von mehr als der Hälfte der Ganglienzellen. Bei selektivem Ausfall der äussern Haarzellen war meistens nur eine zahlenmässig verschwindend kleine Reduktion der Neurone zu beobachten in Ausnahmefällen kam es aber auch bei offensichtlich intakten innern Haarzellen zu einem massiven Zerfall von Nervenfasern in der Lamina spiralis ossea Die Mehrzahl der peripheren Neurone scheint deshalb den innern Haarzellen zugeordnet zu sein. Eine befriedigende Erklärung für die diskrepanten Einzelbefunde steht jedoch noch aus

3 Die unmyelinierten Spiralganglienzellen des Meerschweinchens lassen sich nicht einseitig den äussern Haarzellen zuordnen die beiden Zellpopulationen zeigten weder nach Kanamycin noch nach Knallexposition ein signifikant unterschiedliches Verhalten

4 Morphologisch zeigten geschädigte Spiralganglienzellen im Frühstadium ein Bild, welches vergleichbar ist mit der primären Reizung wie sie in Spinalganglien

nach Läsion der Axone oder Dendriten auftritt Es kommt zur Schwellung des Kerns, der oft randständige Nucleolarsatellit wird grösser und lockert sich bis zur Bildung von Vakuolen auf das ribosomenreich gewordene endoplasmatische Reticulum sammelt sich vorwiegend im Bereich der Zellpole während die übrigen Zellorganellen eher in Kernnähe zu finden sind Im Zytoplasma der Satellitenzellen wachsen sich die Mitochondrien zu Riesenmitochondrien mit unregelmässigen Cristae aus Die Myelinscheide legt sich vermehrt in Falten und scheint im Bereich präexistenter Unregelmässigkeiten myelinierte Einschlusskörper abzuspalten. Einschlusskörper aller Art sind vor allem in den zytoplasmatischen Schichten der Satellitenzellhülle aber auch in den Ganglienzellperikarya zu beobachten.

IV ABSTRACT

This paper describes a study of the morphology of normal and pathologically altered spiral ganglion cells. Embryology, anatomy and histology of the spiral ganglion are reviewed, and the ultrastructure of the spiral ganglion cells is discussed in detail. Special attention is given to the satellite cell sheath and to the various inclusion bodies. Although only a few species have been studied so far, two different ganglion cell types have been distinguished in several animals with respect to cell size, myelin sheath type and character of perikaryon. Unfortunately, the two cell types are not alike from one species to the other. Only in the guinea pig is the difference between the two cell types so distinct as to provide a basis for experimental work. In this species the unmyelinated cells comprise 10% of the total cell population. They are smaller in size than the myelinated cells and typically display a fine filamentous perikaryal structure. They are easily recognized in phase contrast sections.

The pathology of the peripheral cochlear neurons following damage to the end organ has been studied in guinea pigs. In animals exposed to impulse noise and in animals injected with kanamycin, the extent of the damage to the organ of Corti has been assessed by the surface specimen technique and has been compared with damage in corresponding spiral ganglion areas as seen in phase contrast sections and by electron microscopy.

Animals exposed to the damaging effect of gun-shots showed heavy damage to the organ of Corti, followed by retrograde degeneration of the peripheral neurons proceeding centrally to involve the spiral ganglion cells and eventually the nerve fibres of the acoustic nerve.

In kanamycin injected animals, the process of degeneration is progressive over a considerable period. The damage to the spiral ganglion is maximal in the apical region. This drug appears to have a direct toxic effect on the spiral ganglion cells as well as on the hair cells of the organ of Corti.

In regions where all outer hair cells but no inner hair cells have been destroyed there is usually a negligible loss of neurons in the corresponding area of the spiral ganglion, however, in a few specimens, severe damage was noted among the myelinated nerve fibers of the spiral osseous lamina, even though no loss of inner hair cells was seen.

In no instance did the percentage of lost unmyelintated cells significantly exceed the percentage of degenerated myelinated cells. They appear not to be particularly related to the outer hair cells. It can be concluded that their behaviour following noxious stimuli is no different from that of their myelinated counterpart.

The process of degeneration as it affects the cells of the spiral ganglion, is described and illustrated. It is compared with the "primäre Reizung" as it is observed in spinal ganglion cells after lesions to their axons or dendrites.

The question as to why certain ganglion cells survive while others die remains unsolved. It is not known what changes in the organ of Corti "trigger" the eventual degeneration of the associated neurons.

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FROM THE OTOLARYNGOLOGICAL HOSPITAL UNIVERSITY OF HELSINKI
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SUPPLEMENTUM 227

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Histology histochemistry and exfoliative cytology

by

EINO HOLOPAINEN

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CONTENTS

I INTRODUCTION AND OBJECTS OF THE INVESTIGATION

Mucosal biopsy is generally considered a method f choice to confirm the diagnosis in many nasal disorders. Histological investigations of nasal mucous membrane ha e been performed indeed, since th early nineteenth century The development of histochemistry during the last few decades has opened up new wa s f evaluation of the significance f histological observations However practical difficulties limit th use f biopsies in ordinary nasal diseases.

Opinions on the alue of cytological investigation of nasal secretion as a diagnosti tool vary considerably in the l terature Although the exfoliated free cells in th secretion of th respiratory tract ha been in estigated microscopically since the beginning f the nineteenth century reliable techniques were not est blished, however until the nineteen forties through the work of *Papanicolaou (1942)* Nasal exf liatn cytology has been found to be very useful in the diagnosis f tumours and of nasal allergy As early as 1927 *Eyermann* pointed out that eosinophilia in nasal secretion is a sign of alle gic affection, and his observation has later been conf rmed by others (.g *Hansel*, 1929 and *Shambaugh*, 1945) The n estigations made by *Bryan* and *Bryan* (1950 1952, 1955 1959 and b) ha e significantly widened the use f exfoliativ cytology in various nasal diseases. Besides the eosinophilic cells they have paid attention to the appearance f epithelial cells and mast cell in nasal secretion in infectious and allergic nasal diseases.

The etiology and specific treatment of trophic rh nitis ha remained unsolved problems. The disease is still ery embarrassing and in liding disorder to the patient because of the crust f rmation nd the accompan ing unpleasant fetor Nasal histology in trophic rhinitis wa thoroughly investigated in the early twentieth century and some sporadic histochemical observations h been done in recent years. There re however only few comments in th literature n the exfoliativ cytology in atrophi rhinitis (*Schönemann* 1902 *Lautenschläger* 1926 *Holopainen*, 1967 a and b) and no systematic in estigation h s been carried out. Neither has the histology nor the histochemistry of the mucous membrane been investigated in relation t th exfoliativ cytology in nasal secretion in this disease

The main purpose f the present stud is to illustrate the relationship between the histological and histochemical changes in th mucous membrane in trophic rhinitis. on one ha d, and the cytological picture f the secretion and wiped material, on the ther Furthermore the object of the study will be to find out the alue of cyt logical investigation of nasal smears fo an early and accurate diagnosis in atrophic rhinitis. Finally the observ tions will be discussed from the point of iew f the pathogenesis f th disease

II GENERAL MATERIAL AND METHODS

The study consists of a total of 103 patients with atrophic rhinitis examined and treated at the Otolaryngological Hospital of the University of Helsinki during the period 1961–1967. Biopsies and cytological samples were taken at the same examination from every patient. Subsequently a sample was taken for bacterial culture.* Additionally biopsies were taken from 30 patients without nasal symptoms for comparison. For the same reason cytological samples were taken from 98 patients without nasal symptoms. In order to check the appearance of the respiratory epithelium in different parts of the nasal mucous membrane, 9 inferior and 8 middle turbinates from cadavers were studied.

In about half of the patients with atrophic rhinitis histological samples were taken only from the inferior turbinate, whereas in the rest of the material samples were taken both from the inferior and the middle turbinates. The biopsy was performed to the medial ridge of the turbinate about 1/2 to 1 cm posteriorly to the tip of the concha. The tissue specimen was fixed immediately in neutral or 10 per cent formalin solution. On sufficient fixation (2–5 days) the specimens were embedded in paraffin and serial sections at an average of 5 microns were cut perpendicularly to the free surface.

The cytological sample was taken from the same side as the biopsy was to be performed on. It consisted of cells already exfoliated in the secretion and of epithelial cells obtained by lightly wiping the surface of the middle and inferior turbinates. When taking the samples a cotton wiper or a platinum loop was used, and special care was taken to avoid contamination of the specimen with squamous cells from the nasal vestibule.

A Histological and Histochemical Staining Methods

The following staining methods were used:

1. *Van Gieson's* picrofuchsin in combination with *Weigert's* iron hematoxylin to demonstrate the overall morphology of the mucous membrane and, especially, to stain collagen fibers.
2. Hematoxylin and eosin to demonstrate the overall morphology and the tissue eosinophils.
3. *Weigert's* resorcin-fuchsin stain to demonstrate elastic fibers.
4. Silver reticulin stain according to *Nassar* (1961) to demonstrate reticulin fibers.
5. Periodic acid Schiff (PAS) reaction (using *de Tomasi's* (1936) Schiff reagent) to

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* The bacterial cultures were done in the State Serum Institute, Helsinki, Finland.

demonstrate 1,2 glycol groups. When no reaction indicating acid groups was found in the PAS-positive material, the tissue samples were considered to contain neutral mucosubstances or glycogen. The presence of glycogen was tested by using the diastase digestion (1 mg/ml diastase Merck in 0.1 M acetate buffer pH 6.0 at 37° C for one hour).

6. *Hale's* colloidal iron method at pH 2.5 according to *Ritter* and *Oleson* (1950) to demonstrate free acid radicals in mucosubstances; alternatively Alcian Blue (or Astra Blue) at pH 2.5 was used for the same purpose.

7. Toluidine Blue (*Kraemer's* and *Windrum's* (1961) modification) and Azure A to demonstrate metachromasia at controlled pH levels and to visualize the mast cells.

8. Triple stain according to *Himes* and *Moriber* (1956) to demonstrate simultaneously mucopolysaccharides, proteins and desoxyribonucleic acid.

9. Some additional methods were used in connection with the methods mentioned above. Further differentiation of acid groups was achieved by selective blocking of carboxyl groups with $SOCl_2$ methanol methylation (*Korhonen* 1967). Because consequent acid hydrolysis can cause difficulties in the interpretation of the results in the above-mentioned procedure, the CEC (Critical Electrolyte Concentration) principle was employed (*Scott* and *Dorling* 1965). Hyaluronidase enzyme digestion (50 IU/ml hyaluronidase preparation Luronase® Bayer in 0.1 M acetate buffer pH 6.0 at 37° C for 4 hours) was used to differentiate hyaluronic acid and chondroitin sulphates A and/or C from other acid mucopolysaccharides.

It would have been ideal to measure the thickness of the epithelium and the connective tissue membrane exactly. However, it proved to be impossible to handle the small biopsies during the histological processing in such a manner that the section would have been cut completely perpendicularly to the free surface. It was therefore considered more adequate to estimate the thickness visually and to make only rough measurements with an ocular micrometer. Moreover, the thickness of the connective tissue membrane would have been difficult to measure as the borderline between the thin membrane and the lamina propria was mostly unclear.

The following principles were applied when evaluating the histological sections. An epithelium thickness (measured by using ocular micrometer) of over 900 microns was considered to be hyperplastic. When hyperplasia was present throughout the specimen, it was recorded as total, and when it appeared only locally it was marked as partial. The same terms were used for the recording of metaplasia. Increase in degree of metaplasia was graded as follows: beginning stage, moderately advanced, and advanced. The thickness of the connective tissue membrane was graded as thin when thinner than 5 microns, as moderate when between 5 and 15 microns, and as thick when thicker than 15 microns. The thickness of the basement membrane could not be measured in microns. The mononuclear cell infiltration in the lamina propria was described as diffuse when it occurred throughout the specimen and as local when the cells appeared only in local groups. The number of the cells was not counted, but usually they were estimated roughly as representing few, moderate and many. The number of eosinophils was recorded ... a ... *H*... and *Neuhold* (1960) method was used to count the number of ... in a microscope field of 20 × 10 magnification. Altogether ... fields were ... ded ... random ...

different levels of the tissue in every specimen. Less than two cells per microscope field was considered as normal whereas more than four was regarded as numerous. The number of glands was also estimated in the comparable terms few moderate and many The quantity of collagen and elastic fibers was given in comparable terms.

B Staining of the Cytological Smears

The methods used were as follows

1 *Papanicolaou* staining (1937) to demonstrate changes in the epithelial cells

2 Eosin methylene blue staining to demonstrate neutroph lic and eosinophilic leukocytes and bacteria

3 *Wright*'s staining (1902) especially to demonstrate mast cells, but also neutrophils, eosinophils and bacteria

4 Triple stain (*Himes* and *Moriber* 1956) to demonstrate DNA mucopolysaccharides and proteins in the cells

5 Fluorescent acridine-orange staining (*v Bertalanffy* and others, 1956 and *Dart*'s and *Turner's* modification 1959) to demonstrate simultaneously the presence of DNA and RNA in the cells.

In the microscopical evaluation of the slides the appearance of hematogenic cells and epithelial cells as well as bacteria was recorded The hematogenic cell elements were recorded as none, few moderate or many The quantity of epithelial cells and bacteria was recorded similarly

C Suggestions for Cytological Technique as Applied to Nasal Secretion

It wa observed during the present study that in order to obtain first-rate and reliable preparations certain special procedures had to be introduced and strictly followed when examining nasal secretions. Among them the following circumstances were found to be the most essential for the preparation of a good sample composed of cell material from both the surface of the mucous membrane and the secret on.

– The nstrument (a cotton wiper or a platinum loop) must be very delicate to avoid contamination with cell material from the nasal estibule

– The surface of the mucous membrane should be w ped with a very light hand to avoid blood contamination.

– The material should be spread on to a clean slide with great care and it should be fixed immed ately without any drying

– The samples shou ld be fixed f r 30 to 60 minutes in ether alcohol solution (equal part of 95 per cent th yl al hol and ethyl ether)

DNA = deso ribo le l

RNA = ribonucl ac l

— The staining of the fixed smears should be performed within a few days.

— With a Carbowax treatment (*Ehrenreich* and *Kerpe* 1959) it was possible to store the smears even for several months before staining without any significant damage to staining characteristics or to cell structure.

Staining methods

1 If a choice were mad of only one staining method, *Wrights blood stain* would prove to be the most useful With this method it was possible to differentiate hematogenic elements (neutrophils, eosinophils, mast cells and lymphocytes) as well as epithelial changes in the same specimen.

Staining solution Dissolve Wright blood stain (can be obtained commercially) in absolute methyl alcohol to a 0 1 per cent solution. For differentiation use Sörensen s phosphat buffer pH 6.4

Staining procedure:

Place the slide in 80 per cent ethyl alcohol solution for 10 to 15 minutes.
Drop 10 drops of stain on to the lide for 15 seconds.
Drop 10 drops f buffer n to the slide for 15 seconds.
Rinse in distilled water and dry in air

2 When more detailed information about the characteristics of epithelial cells is necessary *Papanicolaou staining method* is no doubt the method of choice. In the present work the following modification of it wa worked out and found to give the best results.

Staining solutions and procedure

Fix the slides in concentrated ether alcohol f at least 30 minutes or by using the Carbowax method.
For hydration dip 3 times quickly in 96, 80 70 50 per cent ethanol.
Rinse quickly in distilled water
Stain with *Harris* hematoxylin solution for 2 minutes.
Rinse quickly in distilled water
Rinse quickly in HCl sol tion (0.25 per cent water solution)
Rinse under running tapwater for 5 minutes
Rinse for 1/2 minute in each of 50, 70, 80, 90 per cent ethanol solutions.
Stain with Orange G-(OC 6) solution for 2 minutes.
Rinse 3 times quickly in each f 3 bowls f 96 per cent ethanol.
Stain with polychromic solution (EA 50) for 2 min tes.
Rinse quickly in 3 bowls of 96 per cent ethanol.
For dehydration and clearing rinse in 2 bowls f concentrated alcohol
Rinse in 2 bowls of xylol for 5—15 minutes.
Rinse in toluol.
Fit the slides with coverglasses mounted with a suitable synthetic medium.

Although the staining steps of the modified method are noticeably shorter than those of the original *Papanicolaou* method, the morphology of the nasal cells is extremely clearly visible. In the blue staining, ammonium hydroxide was used at first, but HCl solution was later found to give the cytoplasm a much brighter colour

3 *The eosin methylene blue staining method* is the quickest and simplest when neutrophils and eosinophilic leukocytes are to be differentiated. It was possible to obtain excellent staining even after the smears had been stored for a long time after fixation. Even when stored for a year the eosinophils and neutrophils could easily be differentiated.

Staining solutions a) Dissolve 0.5 gr of eosin yellow (Merck) in 100 gr of methyl alcohol, and b) dissol e 0.5 gr of methyl coerul medic (Merck) in 100 gr of methyl alcohol.

Staining procedure
Fix the smears in ether alcohol.
Cover the specimens with eosin staining solution for 1 minute.
Add an equal amount of distilled water for 1 minute
Rinse quickly in distilled water and in 96 per cent ethanol.
Drop 10 drops of methylene solution on to the slide for 15 seconds.
Add an equal amount of distilled water fo 15 seconds.
Rinse quickly in distilled water and in 96 per cent ethanol
Dry in air

4 In addition. *Triple stain* as modified by the *Bryans* and *Smith* (1964) was also used in the present work to demonstrate mucoid substances in the cells and the mucin of the nasal secretion

5 Finally *the acridine orange fluorescent method* was used to illustrate DNA and RNA alterations in the cells as has been described in an earlier work (*Holopainen*, 1967 a)

III SYMPTOMFREE NOSE

A Earlier Investigations

The border between the vestibular and respiratory portions of the nasal cavity varies greatly individually in a normal nose *Eggston* and *Wolff* (1947) are of the opinion that the older the person is, the farther back the stratified squamous epithelium extends from the nasal vestibule There are differing opinions as to how frequently and how much squamous epithelium is found in the respiratory portion of the normal nose. According to *Schonemann* (1902) and *Oppikofer* (1906) over 60 per cent of normal noses have islands of squamous epithelium in the respiratory portion of the inferior and middle turbinates. *Charlton* (1907) and *Schumacher* (1925) on the other hand, state that the appearance of squamous epithelium in the respiratory portion of the normal nasal mucous membrane is always a sign of irritation and thus a pathological finding.

The respiratory epithelium is pseudostratified and columnar Its thickness varies physiologically depending on its site in the nasal cavity but most authors consider thickness of more than 200 microns pathological (*Schufferdecker* 1900 *Oppikofer* 1906 *Wagemann*, 1964) True stratified epithelium is regarded as pathological appearance in the nasal mucous membrane (*Runge* 1928)

The epithelium of the nasal mucous membrane consists of three cell types ciliated columnar cells, goblet cells, and basal cells ("Faden Ersatzzellen") *Sternberg* (1924) and some others consider the columnar cells and the goblet cells identical, and it is, indeed, still unclear whether these cells are able to interchange. According to *Messerklinger* (1958) both cells develop from the basal cell. The appearance of the epithelium may vary considerably due to functional changes (*Messerklinger*), and especially the number of goblet cells may fluctuate noticeably within normal limits. When they are abundant, so called intra-epithelial glands develop. Earlier these were regarded as pathological structures but later research considers them normal (*Järvi* 1935 *Messerklinger* 1958)

The epithelium rests on a connective tissue membrane (CTM). The statements in the literature are controversial as to whether the CTM should be considered identical with the basement membrane (BM) or not. In earlier investigations the two membranes were obviously considered identical. However histochemical and electron microscopic investigations (*Leblond* and others, 1937 *Ham*, 1966) define the BM as the very thin PAS-positive layer close to the epithelium, which is not visible in ordinary histological stainings, and in the quite recent literature the name of basement membrane is reserved for the amorphous thin layer (500–2000 Å) next to the epithelium and the rest is regarded as part of the connective tissue (*Rhodin*, 1967) In the present work the homogeneous connective tissue layer which lies beneath the epithelium is

called the connecti e tissue membrane, and only the PAS-positi e part of it close to the epithelium is referred to as the basement membrane

According to *Schiefferdecker* (1900) the CTM of the nasal mucosa has no constant structure, but is changing all the time like a dynamic element, and so its thickness is sometimes reduced and sometimes increased. *Messerklinger* (1950) presents an interesting theory according to which the abundance of the so called hyaline substance in the membrane is a sign of an antigen antibody reaction.

Lamina propria (tunica propria or stroma) is an important part of the nasal mucosa in physiological as well as in pathological processes (*Naumann* 1964) Loose connective tissue is composed of collagen and elastic fibers and additionally of reticulin fibers, which are closely related to the collagenic fibers (*Ham* 1966) The stromal lymphocytes usually lie close to the epithelium diffusely or in groups. This part of the lamina propria is very often called the lymphoid layer (*Hagemann*, 1964) Normally these cells are always found in healthy mucous membrane although they are not so numerous. The same holds true for neutropl lic leukocytes and plasma cells. Only a few eosinophilic leukocytes appear close to the epithelium and a few mast cells lie a l ttle deeper in the lamina propria, mostly around the vessels.

The glands in the normal nasal mucous membrane are sero-mucinous in *Brunner's* op nion (1942) According to *Hagemann* (1964) mucous glands dominate in the healthy nose. In pathologic mucous membrane on the other hand purely mucous or purely serous glands dominate The number of glands n the normal epithel um varies considerably but *Hagemann* gives 150 per square cm as an average, their number decreasing towards the nasal pharynx.

Of the blood vessels the arteries run from the deepest parts of the mucous membrane perpendicularly to the superficial parts of the mucous membrane forming a subep thelial capillary net. where the veins originate

Messerklinger (1960) used PAS-reaction and *Feyrter* staining (*Feyrter* 1936) to study the mucosubstances in the epithelium of the nose and the pharynx He divided the tissues giv ng positi e reaction into two groups 1) the goblet cells, the glands, and the mast cells 2) the intercellular spaces and the connective tissue around the vessels and the glands In the second group the positi e reaction disappeared when the tissue wa treated with hyaluronidase. *Buchholz* (1958) used a comb nation of PAS and Alcian Blue when studying normal nasal mucous membrane biopsies and found hyaluronidase sensitive material only n the wall of the vessels *Taylor* (1958) found abundant PAS-positi m terial in the ep tl elium and the mucous glands The connect e tissue membrane wa PAS-negative *Weisskopf* and *Burn* (1958) studied m sco ds in the connective t ssue ground substance of the normal mucous mem brane W th Toluidine Bl e the goblet cells stained metachromatically at pH 5, whereas the ground substance re ained rthochromatic After treatment with hyalu ron dase onl n ast cell and essel w ll reta ned metachromasia.

Only a few t teme t on th f l t cyt logy f symptomfree nose can be found in the literat re *T rrig* 1)) t t d h t there were ery few cells in normal nasal secretion. ma l ynl η l n utrop h l Although he also reported the

presence of ep thelial cells, he did not describe them more closely *Hilding* (1930) made observations of cell elements both in normal and infected nasal secretion. According to *Urfer* (1937) the borderl ne between normal and inflammatory secretion was not possible to distinguish. *Messerklinger* (1954) took samples by wiping the membrane with a platinum loop and used phase contrast microscope to study living epithelial cells.

B Material and Methods

In order to acquire information about the appearance of squamous epithelium in the respiratory portion of the nasal mucous membrane 9 inferior and 8 middle turbinates taken from 10 *cadave s* were studied histologically They were from subjects who according to previous clinical history and examination had no apparent signs of infection in their nose The turbinates were serially sectioned and every 50th section was examined and the type of epithelium registered.

The *b opsy* material consisted of a total of 54 specimens (30 from th inferior tur binate and 24 from th m ddle turbinate) They were obtained from patients hospitalized for othe reasons than nasal diseases and none f the patients had any nasal symptoms. For a considerable number of the patients (11) the di gnosis was chronic tonsillitis. Uninfected traum tic septum deviations (5) were lso considered symptomfree and 7 patients wer hospitalized only fo observation

The *cytolog cal* material was obtained from patients who were in the hospital without subjecti e nasal symptoms. The main part of them (34) were hospitalized for tonsillectomy 14 patients for chroni otitis. 14 patients for otosclerosis and 18 for miscellaneous reasons. In add tion, 18 healthy members f the hosp tal staff supplied material for in estigation. The cytological sampl taken from the same side as the biopsy was smeared on to 3—4 slides for different stainings. At the same examination sample was taken for bacterial culture from the same sid of the nose.

C Results

In the *aut p y* m terial the respiratory epithelium extended as far as the anterio tip f the inferio turbinat in 5 cases, whereas the borderline between the respiratory nd estibular ep thelium varied in the remaini g cases, being located 3—10 mm back wards from the anterior tip of the inferior turbin te The epithelium of the anterior tip f the middle turbinate was of the respiratory type in 2 cases, whereas in the remain ng cases the quality of the epithelium resembled th estibula one. No islands of squamous epithelium were found in 4 inferior turbinates and 2 middle turbinates In the main part of th material the number f islands was wery small, constituting in most cases less than 5 per cent of th epithelium. Mainly the epithelium was pseudostratified and columnar and most of th columnar cells had preserved their



FIG 1 — *Ciliated pseudostrati fied columna epithelium in symptomfree nasal mucosa. Van Gieson 520 × (The substage dia phragm of the microscope restrict ed to induce refraction.)*

cilia (Fig. 1) In one inferior turbinate the major part of the epithelium consisted of columnar stratified epithelium without cilia. Among the epithelial cells, goblet cells were abundant, their number comprising almost 50 per cent of the epithelial cells in 2 cases. The results of the autopsy material are presented in Table I

TABLE I — Histological turbinate findings in 10 cad ers

Years f ag	Amou t of columnar cell epithelium in per cent		Amount of squamous cell epithelium in per cent		Distance of border f resp epit. from the tip in mm	
	Inferior turbin te	Middle turbinate	Inferior turbinate	Middle turbinat	Inferior turbinate	Middle turbinate
17	100	99	0	1	xt. tip **	ext. tip
20	—	90	—	10	—	indistinct
22	97	98	3	2	ext. tip	3
22	100	100	0	0	ext. tip	ext. tip
50	95	98	5	2	7	2
54	99	70	1	30	3	6
70	100	95	0	5	ext. tip	5
75	50	—	50	—	10	—
unrecorded	100	100	0	0	ext. tip	ext. tip
unrecorded	95	—	5	—	5	—

The percentage expresses the amount of columnar cell respectively squamous cell epithelium f the entire inferio a d middl turbi tes.
ext. tip = extends t the tip

The results of the *h stolog al* examination of the biopsies from symptomfree noses are gi en in Table II A can be seen, ciliated pseudostratified p th lium was found in about half f both he nferior and the middle turbinates. In one third of the



FIG 2. — *Moderately thick connective tissue membrane (CTM) in symptomfree nasal mucosa*
Van Gieson 190 ×

biopsies no cilia were visible however the epithelium was stratified and columnar Hyperplasia of the epithelium occurred rather often in both turbinates, but even then only locally Metaplasia was present in some specimens, but was mild in degree and extension. The connective tissue membrane was visible in all the specimens and its thickness mostly varied from 6 to 20 microns (Fig. 2) Reticulin fibers were seen in the lamina propria (Fig. 3), especially abundantly in and close to the basement membrane and around the glands. The basement membrane stained unevenly (Fig. 4) and was



FIG 3 — *Reticulin fibers (arrows) in symptomfree nasal mucosa. Numerous glands noticeable in the stroma. Vassar 100 ×*

sometimes completely absent. In the lamina propria local round cell infiltration was present, and *few or some mast cells were seen. Vessels were numerous, and the thick* ness of their walls varied from 5 to 50 microns. Fairly abundant elastic fibers surrounded the vessels. The glands were also numerous (Fig 5) and showed strong metachromasia (Fig. 5) The number of collagen fibers was moderate and in about one fifth of the specimens a slight fibrosis was apparent in the stroma.

TABLE II — Histological findings of 54 biopsies from 30 cases of symptomfree nose expressed in per cent

Epithelial and stromal findings	Inferio turbinat (30 samples)	Middl turbinate (24 samples)
Ciliated epithelium	43	54
Metaplasia	16	12
Hyperplasia	23	12
Increase in thickness of connectiv tissue membrane	13	12
PAS-positivity of basement membran	67	58
Round cell infiltration	15	29
Glandula changes	0	4
Changes in the vessels	0	4
Stromal fibrosis	20	8

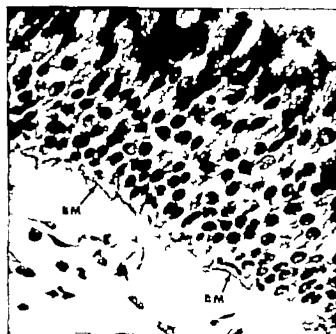


FIG 4 — *Basement mem bran (BM) in symptomfree nasal mucosa. PAS 260 ×*

The results obtained by *histochemical* methods are summarized in Table III, where the degree of staining is visually quantified and the type of metachromasia described (see also Fig. 5)

TABLE III – Histochemical results in symptomfree nasal mucosa

	PAS	Hale Astra Blue	Toluidine Blue (metachr. (alcohol))	Hyaluronidase	$SOCl_2$ methylation/AB	Astra Blue pH 1.0	pH 3.0	pH 4.5	Astra Blue MgCl₂ 1.0 M	0.7	0.4	0.2	0.1
Outer border of columnar ciliated cells in epithelium	+	+	B	B	–	B	B	B_v	–	(+)	(+)	+	++
Mucin in goblet cells in epithelium	+++	++		v	+	B	B	v	–	–	+(+)	++	++
Glands serous	(+)	(+)	B	B	–	B	B	B	–	–	–	–	++
Glands mucous	+++	++	B_v	B_v	+	B	B	B	–	–	+	+	++

Explanation of the marking system

+ = regular
(+) = irregular
B = blue
B_v = blue violet
(B) = irregular blue violet
v = violet

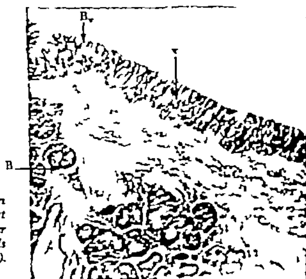


FIG 5. – *Metachromasia in symptomfree nasal mucosa. Goblet cells stained violet (= v) outer border blue violet (= Bv) glands blue violet (= Bv) or blue (= B). Toluidin Blue 90 ×*

The distribution of different cell types in the *cytological* smears is presented in Table IV. Columnar epithelial cells with or without cilia were the most common and constant cell element. By applying the wiping method it was often possible to obtain fresh, well-preserved ciliated epithelial cells (Fig. 6). A well-preserved epithelial cell was oval in shape and about 10 microns in length, one end being slightly broader than the other. The broader end contained a flat thickened cell membrane (the cuticular plate or terminal bar) bearing many fine cilia. The cytoplasm was homogeneous but sometimes contained fine vacuoles. In *Papanicolaou*'s method the cytoplasm stained

TABLE IV. — Cytological findings of the nasal smears of 98 cases of symptomfree nose expressed in per cent

Cell elements	none	few	moderate	many
Columnar epith. cells with without cili	0	14	56	30
Goblet cells	35	36	25	4
Basal cells	0	0	0	0
Squamous epith. cells	88	5	5	2
Metaplastic cells	89	8	3	0
CCP cells	72	17	10	1
Neutrophils	49	26	18	7
Eosinophils	96	2	2	0
Mast cells	97	3	0	0
Lymphocytes	80	11	8	1
Bacteria	82	11	6	1

Defined in the text at page 44



FIG. 6. — *Well-preserved ciliated epithelial cells in nasal secretion. Papanicolaou 520 ×*

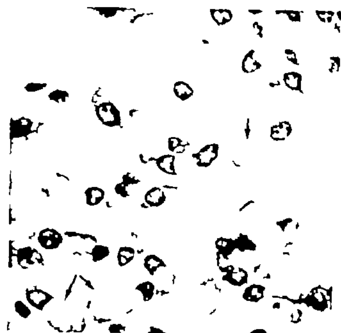


FIG — *Nasal smear with goblet cells (arrows) Papanicolaou 520 ×*

blue or bl e green. Th cuticular plat and th cilia usually stained densely pink. The nucleus wa oval and vesicular hromatin clum w well visibl nd the nucleoli occasionally prominent. Th cili ted cell app ared both singly a d in sheet or clusters.

Goblet cells were frequently present in the sam les (Fig 7) ... they ppeared as high columnar cells but without cili They were si ilar t the ili ted ll in size and always contained cytoplasmic v cu les



FIG 8 — *Sq amou ep th lial cells in nasal sm ea Papanicolaou 910 ×*

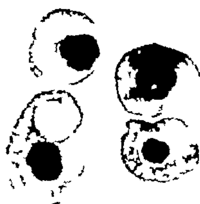


FIG 9 — *Different forms of metaplastic cells in nasal smear*
Papanicolaou 1000 ×

Cells exfoliated from the inner stratum of the epithelium i.e. the basal cells, were not found in this material.

If the sample had been carefully taken with a delicate instrument like a platinum loop, the risk of contamination with squamous epithelium was not too great. Altogether 86 smears did not contain squamous epithelial cells at all, 10 smears had very few or a moderate number and only in 2 smears were fairly many present. When squamous cells were found, they were without exception of the superficial type, being large and thin in shape and having small *nuclei* and acidophilic cytoplasm (red in *Papanicolaou* staining) (Fig. 8).



FIG 10 — *Rural form of epithelial cell (CCP) with pyknotic nucleus (arrow) in nasal smear*
Papanicolaou 1330 ×



FIG 11 — *Mast cells in nasal smear Wright 1260* ×

Metaplastic cells were present in a few smears. They had a d tinct outline and dense basophilic cytoplasm. The size of the nucleus aried accordi g to the size of the cell, but the nucleo-cytoplasmic ratio remained con tant (Fig 9)

In some smears a few viral forms f epithelial cells (CCP cells, see p 44) were found (Fig. 10)

The polymorphonuclear neutrophil w s the most common hemat genic cell appear ing in half f the specimens. Eosinophili leukocytes well as mast cells (Fig 11) were very scarce throughout the whole material. Lymphocytes w re present in one fifth of the specimens.

Bacteria were not isible in the smears from symptomfree nose The bacterial cu lt re was negativ in 80 cases. saprophytes were found in 12 cases nd n 6 ases poorly growing pathogenic bacteria were found.

Sex and age had no significance fo the cytological picture n symptomfree nose Neither did the cellular pictures of smokers d ffer noti eab ly from those of non smokers.

D Discussion

The present *autopsy* material is limited and does not allow any general conclusions to be drawn. However the investigation supports the earlier view of the variability of the borderline between the respiratory and the vestibular epithelium. Moreover occasional islands of squamous epithelium were present among the respiratory epithelium In consequence of this finding, the biopsies of the present investigation were performed as far back as possible in both th inferior and the middle turbinates.

The size of the *biopsy* material is limited, too, owing to the fact that the manipulation of the mucous membrane is not completely harmless to the patient. Nevertheless, it gi es a picture of reference of the symptomfree nasal mucosa. In many respects the structure of the mucous membrane was very close to the description of normal mucous membrane as found in the literature However it could be clearly demonstrated that well preserved ciliated epithelium s by no means a constant finding in symptomfree nose. Although one takes into account that lesions easily occur during the biopsy well preserved ciliated epithelium appeared remarkably sparsely stratified columnar ep thelium being a more frequent finding This should apparently be considered as a physiological appearance probably caused through the irritation of inhaled air currents. On the other hand, the frequency of squamous epithelium was quite low In about one fifth of the specimens the number of mononuclear cells and in 2 samples the number of mast cells exceeded normal limits, and in some cases slight fibrosis appeared in the stroma.

The present *histochemical* results showed that all the PAS-positive material in the symptomfree nose was resistant to diastase digestion. This ind cated that glycogen was absent from specimens of normal mucosa. The strongly positive PAS-reaction in the outer border of the epithelium as well as in goblet cells and mucous glands suggested the presence of neutral mucosubstances. The positive Hale-reaction *) on the other hand, indicated the presence of acid radicals in the outer border of the ep thel um, goblet cells and mucous glands. The material in goblet cells and mucous glands was resistant to $SOCl_2$ methanol methylation pointing to the presence of sul phat ester groups. The presence of carboxyl groups in the outer border of the epithelium w suggested by th methyl tion experiment, and metachromasia in Toluidine Blue and Azure A beginning at pH 4 5. The positiv Azure A reaction at pH 1.6 was a further evidence of sulph te ester groups in the goblet cells. Additional evidence of this mod of distribution was obtained by the CEC technique.

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*) Identicall w th the Hale-rea tion, the Tripl stain also showed the presence f mucosubstances in th ep theli m The Alcian Blue t ming t pH 2.5 is generally considered more specific method th the Hal staining method I the case f the nasal mucous membran the res lt re d al Beca se f th sharper ppearance f the staining the Hale-reaction was me tl ned

Although the presence of sulphate groups in mucous gland was demonstrated with methylation, the metachromasia in Azure A ppeared only at relatively high pH (4.5). This could be due to greater distance between the acid groups or to th lower molecular weight of the mucin in mucous gland as compared to that of goblet cells. A further evidence of thi s the intermed at CEC alue (0.4) of muc n in mucous glands, suggesting lower molecular we ght of this material (*Scott* and *Dorling* 1965). All the carbohydrate reactions in the serous gl nds were weak, pointing to th fact that there were small amounts of this material in tl eir secretion.

When the results f the histochemical methods for the acid mucopolysaccharides were interpreted, a possible masking f acid radicals by protein at low pH lues h d to be considered (*Szirmai* and *van der Linde* 1965). A relati ly high pH alu (5.8) used in the present investigation in the CEC method reduced this effect. The use of increasing concentrations of $MgCl_2$ made it possible to regulat the dye binding of different acid groups, and thus carboxyl nd sulphate groups could be differentiated. The hyaluronidase enzyme digestion did not ffect the Toluid ne Blue meta hromas in the epithelium nd in the glands. Neither did the enzym d gest on affect the PAS-positi material in the ep thelium. This h luronidase resistant Toluidine Blue metachromasia pointed to the fact that th re w re no hyaluronic acid and chondroitin sulph te A and/or C n the symptomfree mucosa.

It was evident from the material that the column r ep th l l cell wa the most common cell element to be found in the *cytological* samples from symptomfree noses. A considerable part of these cells were well-preserved and ciliated. In this respect the cytological picture of symptomfree nose clearly differed from what could be predicted on the basis of the histology where the appearance of ciliated epithelium was not too common. Goblet cells appeared in lmost all cases, nd their appearance might be regarded as a sign f the vit lity f the mucous membrane. The sparse ppearance of metaplasti and squamous cell indicated, in the first pl ce that a nasal cytological sample can be taken without contamination with the cell from the nasal estibule nd, in the second place that the islands of squamous epithelium are not numerous in symptomfree nasal m ou membrane. In 5 per cent of the cases the presence f fairly bund nt neutroph ls in the secretion probabl indicated an infection, although the patients had n subjective symptoms. There were no cases of increased secretion eosinophil in the material.

IV ATROPHIC RHINITIS

Atrophic rhinitis is a chronic nasal disease the pathogenesis of which has not been satisfactorily explained. The etiology of primary or genuine atrophic rhinitis is entirely unknown. *Runge* (1928) divides it into two groups *rhinitis atrophicans simplex* which appears without crusts, and *rhinitis atrophicans foetida sive ozaena*, which is the final stage with crusts and fetor. *Ruskin* (1942) includes in the primary type such kinds of atrophic rhinitis, where alterations appear in the walls of the vessels of the mucous membrane. The secondary type of atrophic rhinitis is in his opinion caused by chronic bacterial infection in the nose.

According to recent investigations the character of atrophic rhinitis might have changed in the last few years. *Taylor* and *Young* (1961) have introduced the new concept of two types of atrophic rhinitis. The first type is characterized by endarteritis and periarteritis of the terminal arterioles as a result of chronic infection in the nose. The second type is characterized by dilatation of the capillaries of the mucous membrane. According to *Taylor* and *Young* the frequency of the former type is decreasing noticeably, the latter type being the predominant one today.

A Earlier Investigations

According to *Jakobi* (1964) the following histopathological alterations are typical of atrophic rhinitis:

- decrease in the thickness of the mucosa,
- metaplastic change of the columnar ciliated epithelium,
- degeneration and atrophy of the goblet cells as well as of the serous and mucous glands,
- increasing thickness of the connective tissue membrane (the number of collagen fibers increases),
- diffuse fibrosis in the mucosa,
- infiltration focuses particularly around the vessels,
- endarteritis of the terminal arterioles,
- rarefaction of the turbinal bone structure.

Epithelial changes. Squamous metaplasia of the respiratory mucous membrane is considered typical of atrophic rhinitis by most authors (*Schuchardt* 1889, *Lautenschlager* 1926, among others). However, most of them agree that a similar change can be found in any chronically infected nasal mucous membrane (*Choleva* and *Chordes* 1898, *Schonemann* 1902, *Oppikofer* 1906). It has therefore been stated that squamous metapla[illegible] [illegible] atrophic rhinitis, but rather a consequence of

it. In serous mucous membrane *Schonemann* (1902) *Runge* (1928) and *Sarén* (1928) observed metaplasia only locally in th form of islands surrounded by transitional epithelium. According to recent investigations by *Messerklinger* (1955) the hyaluronic acid-hyaluronidase metabolism of the mucous membrane is significant fo the devel opment of metaplasia.

Connective tissue membrane and basement membrane Opinions on the structure of the connective tissue membrane (CTM) and its import nce for the function of the mucous membrane vary According to most authors th CTM thickens in chronic infections (*Shambaugh* 1931 *Hollander* 1944) *Eggston* and *Wolff* (1947) stated that the CTM is usually thickened and contain a large amount of collagen in atrophic rhinitis. *Taylor* and *Young* (1961) did not agree with the pinion that the CTM thickens in atrophic rhinitis, but they noticed n th membrane a well-m rked layer f reticulin fibers.

Lamina propria It is known that in n early stage of trophic rhinitis there is abundant mononuclear inf ltration in the lamina propri in add tion t lymphocytes, many mast cells are present, the predominant cell lement being plasma cells. When the mucous membrane is atrophied, the cell infiltration diminishes and hyaline degeneration begins to appear in the cytoplasm of the plasma cells. Simultaneously the number of mast cells increases, whereas that of leukocytes and lymphocytes decreases (e.g. *Sternberg* 1923) In an ad anced stage of the disease Russel's bodies in the plasma cells dominate the histological picture

According to most authors the number f connecti tissue fibers increases in trophic rhinitis. *Sternberg* (1923) states that increase in collagen fibers is very typical of th final stage of atrophic rhinit s, causing fibrosis in the mucosa. *Taylor* and *Young* (1961) did not note an increase of collagen fibers in thei material of atrophic rhinitis.

Most authors are f th opinion th t the changes appe ring in the glands in atrophic rhinitis are not primary *Sternberg* (1923) regarded the so called periglandular infiltrations as characteristic of an early stage of trophi rhinitis. Fatty degeneration is also found in the glands gradually leading t thei complete disappearance. *Runge* (1928) again thought th t th degeneration f the glands, similarly to the metaplasia of the epithelium was caused by the t xic influence in infections.

Opinions on th changes in the wall of th essel vary *Sarén*s (1928) observations pointed to the fact th t the ch nges i the essels are not the primary cause of atrophic rhinitis. H fou d most changes in tl el and in the capillaries and only a few changes in th rteries. *Taylor* and *Young* (1961) did not note signs f arteritis or periarteritis, but in their op nion the l l t tion f tl capillaries is a primary essel change in atrophic rhinitis.

Messerklinger (1958) noted histochemically tl t atrophic rhinitis hyaluronidase sensitive material increases i the met pla tl epithel um, decreasing instead in the intercell lar spaces of the connect tis e nd in the walls of the vessels. Accordin to him met plasi due t the fact tl t the i reasing mucoid substances diminish the permeab lity f the mucous membrane *Hi d hol* (1958) did not find much mucoid substance in tl met pl sti pithell m b t in three cases of trophic rhin t. *H ...* *kopf* (1960) reported n ncrease in the n t f mucosubstances in the ...

propria associated with increased amount of collagen. Of particular interest was the presence of a large number of mast cells. *Taylor* and *Young* (1961) stud ed the nasal mucosa of 14 patients suffering from atrophic rhinitis. They found PAS-positive granules in some superficial metaplastic cells of the nasal mucosa, but not in the deeper layers. Only small variations in the distribution of DNA and RNA were found in the stratified squamous epithelium. The basement membrane when present, was thin and showed PAS-positive reaction. *Bonani* and *Parolari* (1961) found an increase of sudanophilia in the stratified squamous epithelium and in the mucus on the epithelial surface *Gasparini* (1962) found the acid mucosubstances to be decreased in the ep thelium and in the tunica propria of the nasal mucosa. Other mucosubstances decreased greatly in the epithelium and in the connective tissue membrane, while they increased in the tunica propria.

Schonemann (1902) stated that *Valentin* as early as 1887 investigated superficial epithelial cells microscopically in the secretion of some cases of atrophic rhinitis, finding abundant squamous epithelial cells in the nasal secretion in atrophic rhinitis and among the inflammatory cells he noted mast cells. In two previous papers *Holopainen* (1967 a and b) described the general cytologic picture of the secretion of atrophic rhinitis.

B Material

The material consists of altogether 146 biopsies from 103 patients. In Table V the age and sex distribution of the patients is presented

TABLE V – Age and sex distribution of 103 patients with trophic rhinitis

Age	Males	Females
Below 15 years	3	4
15–35 years	8	39
36–55 years	5	27
Above 55 years	0	9
Unrecorded	3	5
Total number	19	84

TABLE VI – Clinical classification of 103 patients with atrophic rhinitis

	Males	Females
Rhinitis trophicans simplex	5	4
Rhinitis trophicans foetida	14	80
Total number	19	84

According t the type of disease the material was composed as presented in Table VI

The number of biopsies taken from both the inferior and the middle turbinates was 43 only the inf r turb nat w b opsied in 58 cases, and only the middle turbinate was the site of the b ps tw V w a mentioned earli r the biopsies, especially those

from the inferio turbinate were taken as far back as possible to make sure that the biopsy should originate in the respiratory portion of the nasal mucous membrane

The cytological material accords with the hist logical material as the samples were collected from the same patients and from the same side of the nose that the biopsy was to be performed on. At th same examination a sample for bacterial culture was taken.

C Results

The ep thelial changes observed *histologically* are presented in Table VII There w re considerable variations in the thickness of the epithelium. It was often locally hyperplastic, and it was thin only in connection with advanced metaplasia. Cylinder columnar epithelium with or witho t cilia was seen only locally and appeared only in a few specimens. Squamous metaplasia was present in most cases either in th inferior or in the middle turbinat (Fig 12 and 13) very often both turbinates were affected simultaneously In about one fifth of the specimens the ep thelium showed metaplastic changes throughout its length, whereas in the main part of th specimens only part of it was metaplastic. Early stages f metapla ia were present in 25 per cent of the specimens, and they w re characterized by tratification as well as fl ttening f the cells (Fig. 14) In about 60 pe cent f the specimens the metaplasia was more advanced, but no keratosis could be seen n the surface layer of the epithelium. Advanced stage of metaplasia with keratosis in the surface layer of the ep thelium was observed in the rest of th specimens, chiefly in the inferior turbinates.

TABLE VII — Epithelial changes in 146 biopsies f 103 pat ents with trophic rhinitis expressed in per cent

Epithelial findings		Inferior turbi t (101 samples)	Middle turbin te (45 samples)	Inferior and middle turbinate simultaneously (45 cases)
Columnar epithelium	with cilia	8		5
	without cilia	11	15	12
Hyperplasi	total	10	0	0
	partial	60	55	55
Metaplasia	total	20	15	5
	partial	73	76	58
Papillomatous struct re		26	18	7
Keratosis		19	4	0

Mucosubstances appeared fairly sparsely n trophied epithelium. When the epithelium wa keratinized, both PAS- and Hale-positi material was bserved in the superfici l cells in 15 per cent f th specimens (Fig. 15) In an ea ly tage f metaplasia tercellular mucosubstances w th the same stain ng reacti ns were isible in 25 per cent f the specimens (Fig 14). 26 per cent f th specimens lacked mucosubst nces in the epithelium. Th more detailed *h t h mi al* differ entiation f the trophied mucosa is presented in T bl VIII t page 31

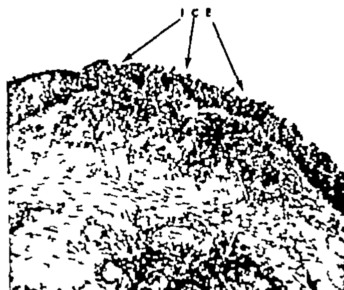


FIG 12. — *Island of columnar epithelium (ICE) in the middle of squamous metaplastic epithelium with focuses of subepithelial and periglandular stromal cell infiltration (white arrows) in atrophic rhinitis V an Gieson 90 ×*

The th ckness of the connective tissue membrane (see Table IX) varied noticeably n different parts of the same specimen, and it was usually ery thin o almost absent (Fig. 16) Only seldom was it thicker than normal. The entire connective tissue membrane did not show positive PAS-reaction, but only the part lying closest to the epithelium i e the basement membrane (Fig. 15) This basement membrane varied in thickness, being mostly thin and always discontinuous.

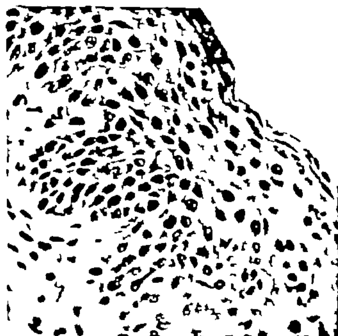


FIG 13. — *Squamous metaplastic epithelium in atrophic rhinitis Higher magnification V an Gieson 380 ×*

TABLE VIII — Histochemical results in trophic rhiniti

	PAS	Hale	Tol idine Blue (metat l ol d)	H al ronidase	SOCl methyl tion/A B	Az re A pH 1.6	Az re A pH 3.0	Az re A pH 4	Alcian Blue MgCl 1.0 M	Alcian Blue MgCl 0.7	Alcian Blue MgCl 0.4	Alcian Blue MgCl 0.2	Alcian Blue MgCl 0.1
Outer border f squamous epith.	+	(+)	B,	B	(+)	B	B	(B)	–	(+)	+	+	+
Mucosubstances in intercellular spaces in squam. epith.	(+)	(+)	(B)	(B)	–	B	B	(B)	–	–	–	–	+
Glands serous	(+)	(+)	B	B	–	B	B	B	–	–	–	–	+
Glands mucous	++	++	(B,)	(B)	(+)	B	B	(B)	–	–	–	+	+

Explanation f the marking system

B = blue B = blue iolet

(+) = irregular (B) = irregularly blue violet

+ = regula

The goblet cells were so occasional that they were omitted from the tabl



FIG 14 — *Hale-positive material (arrows) in intercellular spaces and basement membrane in atrophied nasal mucosa. Hale 190 ×*

Ict O olur Stock) olm) pnl —

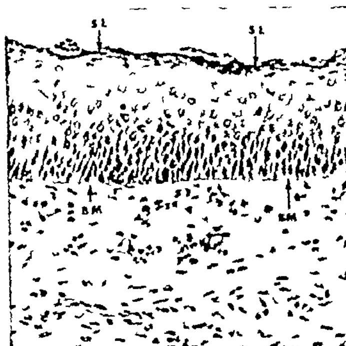


FIG 15 — *Atrophied nasal mucosa with PAS positive material in the surface layer (SL) and in the basement membrane (BM)*
PAS 190 ×

TABLE IX — Histological observations in the lamina propria of nasal mucosa of 103 patients with atrophic rhinitis expressed in per cent

Stromal findings		*Inferior* turbinate (101 samples)	*Middle* turbinate (45 samples)
Connective tissue membrane	thick	17	11
	moderate	26	29
	thin	57	60
Round cells	many	44	67
	moderate	49	51
	few or none	7	2
Eosinophils	many	4	13
	moderate	11	11
	few or none	85	76
Mast cells	many	52	40
	moderate	33	42
	few or none	15	18
Glands	many	20	18
	moderate	31	49
	few or none	49	33
	periglandular infiltration	85	89
Vessels	many	11	9
	moderate	64	33
	few or none	25	58
	perivascular infiltration	92	93
	arteritis	10	2

Among the connective tissue fibers in the lamina propria there was a slight increase in collagen fibers in 41 per cent of the inferior turbinates and in [illegible] per cent of the middle turbinates. In most specimens (62 per cent) the number of elastic fibers was slightly decreased. In the main part of the specimens [illegible] there were abundant reticulin fibers in the subepithelial connective tissue [illegible] and around the glands and the vessels. In 80 per cent of the specimens the reticulin fibers were clumpy (Fig. 17) quite often the connective tissue membrane was discontinuously stained with reticulin stains (Fig. 17)

A stromal cell infiltration could be noticed in most cases (Fig. 12 and 16). Lymphocytes and plasma cells constituted the majority of the cells. They appeared [illegible] ally as a local infiltration in most of the cases ([illegible] per cent). The frequency and distribution of the cells are given in Table IX at page [illegible]. [illegible] occurred sparsely. Total absence of tissue eosinophils was rare, however. The appearance of eosinophils as well as mast cells is presented in Table IX. It can be seen that mast cells in almost every case were more numerous than what can be considered normal (cf. p. 10) and that more than [illegible] of the cases showed abundance of mast cells (Fig. 18). In the present material [illegible] were found.

The number of sero-mucinous glands in the [illegible] was [illegible] in most cases (see Table IX and Fig. 19). In the main part of the cases mucous glands were predominating (70 per cent of the inferior turbinates and 67 per cent of the middle turbinates). Periglandular infiltration was present in [illegible] specimens (Fig. 12 and 19). Cystic degeneration was not very common in the glands, appearing in [illegible] per cent of the inferior turbinates and in 20 per cent of the middle [illegible]. [illegible] fatty degeneration were visible, neither was anything pointing [illegible] noted in the material. In 20 per cent of the specimens [illegible] with PAS and Hale-positive material were visible, in 28 per cent [illegible] and in the rest of the specimens there were only a few glands with [illegible]

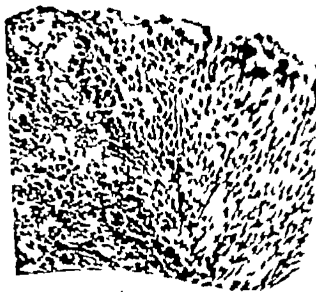


FIG 16. — *Very thin almost absent connective tissue membrane (CTM) and stromal cell infiltration in atrophied nasal mucosa. Van G eson 190 ×*

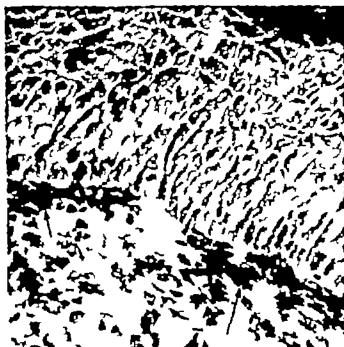


FIG 17 – *Clumpy reticulin fibers (arrows) in atrophied nasal mucosa. Nassar 520 ×*

Few

Moderate

Many

FIG 18. – T s m st ll n n *atrophic hinitis Toluidine Blu 190 ×*



FIG 19 — *Few stromal glands (arrows) with peri glandular infiltration in atrophied nasal mucosa. Cf Fig 3 Van Gieson 90 ×*

Perivascular round cell infiltration was the most comm n change in the vessels in the present material (see Tabl IX and Fig 20) Only in v ry few cases were changes in the terminal arterioles noticeable. Such a change was usually a thickening f the intima, causing a reduction of the lumen of th essel. T tal bstruction of the essel was not found. The thickening f the whole wall of the essel could be observed in 2 per cent of the inferior turbinates. Only in few specimens (12 per cent) there was PAS- and Hale-positiv material around th vessel and also in their walls.



FIG 20 — *Perivascular round cell infiltration in atrophied nasal mucosa. Van Gieson 1.0 ×*

The distribution of various cell elements in the *cytological* specimens is given in Table X. It can be seen that an abundance of neutrophilic leukocytes was a characteristic feature in atrophic rhinitis. Sometimes the appearance of these cells was so abundant that other cell elements were obscured by them (Fig 21) The neutrophils were often broken and their structure was indistinct. Although bacteria appeared abundantly there were only a few leukocytes with phagocytizing activity (Fig. 22, 23 and 27)



FIG 21 — *"Mass of neutrophils in nasal smear of atrophic rhinitis. Papanicolaou 90* ×

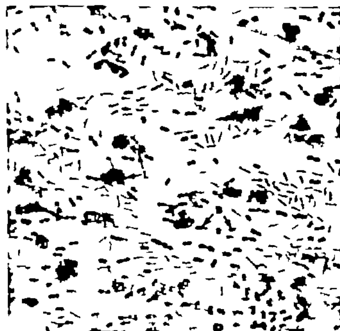


FIG 22 — *Groups of mainly non phagocytizing leukocytes (L) and thick stemmed bacteria (B) in nasal smear of atrophic rhinitis Papanicolaou 940* ×

Eosinoph lic leukocytes were very rare In m ny cases total eosinopenia was noticeable in the secretion, and often only a few eosinophils were present among abundant neutrophils. Only 3 cases showed so large a number of eosinophils that these could be regarded as moderat ly numerous. Six cases were borderline cases with small groups of eosinophils surrounded by numerous neutrophils. The material contained no case where eosinophilic leukocytes would have been the predomin nt cell element in the secretion. Mast cells appeared even more sparsely than eosinophils in the cytological specimens.

The appearance of lymphocytes was sparse in the material. Almost every specimen contained a few lymphocytes, but they never constituted the predominant cell element.

One of the most typical observations was that the columnar epithelial cells constituted only a minor portion of the exfol ated and wiped material. In fact, nearly half of the specimens showed absence of columnar cells, thei number being very small in approximately one third of the materi l Few of these cells had preserved their cilia In some of the columna cells without cil a, the nuclei were frequently large with rather dense chromatin structure.

Goblet cells were infrequent as well, the main part of the material containing none Similarly to the material from symptomfree nose th smears f trophic rhinitis lso lacked basal cells.

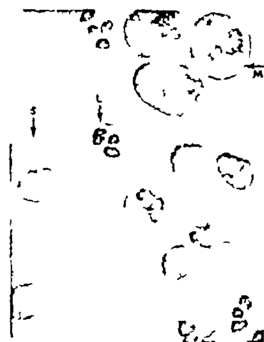
Epithelial cells containing striking nuclear changes, CCP cells (Fig 10, see also p 44) were rather scarce taking into account that most of the samples were taken in the winter season when the frequency of respiratory virus infections is quite high

Met plastic cells constituted one of the most characteristic elements in the cytological picture of atrophic rhinitis. They had a distinct outline, the cytoplasm was dense and stained basophilic or dark reddish in *Papanicolaou* stain. The nucleus was located in the centre and it lso had a distinct outline The distribution f chromatin aried somewhat, the relation between the nucleus and the cytoplasm rem ining constant (cf. Fig 9) The metaplastic cells were easily distinguished, since they appeared in small groups of 5 t 10 cells (Fig. 23) Intercellular bridges were sometimes visible in these cell groups (Fig. 24) In some cells vacuolization of the cytoplasm appeared and the density of the cytoplasm aried in different cells depending on the degree f maturity f the cell (Fig. 25).

Different kinds of squamous epithelial cells were bundant in 70 per cent of the cases f the material. The squamous epithelial cells were mostly the predominant cell lement together with the metaplastic cells, and their number was usually larger than that f the metaplastic cells. The keratinized anucleated squamous epithelial cells rarely ppeared. The cytoplasm f these cells stained yellowish orange with *Papanicolaou* s st ining method and showed a keratin line along the periphery f the cell. The superf cial type of squamous cell was the most common (Fig 23, 26 and 27) These cells had small pyknoti nucleus and in *Papanicolaou* s stain usually a eosinophilic cytoplasm, nd only seldom a basophilic reaction.



FIG 23 a — *Groups of squamous and metaplastic (M) cells and leucocytes (L) in nasal secretion from atrophic rhinitis Papanicolaou 190 ×*



b — *Group of the same cells in higher magnification Papanicolaou 940 ×*



FIG 24 — *Intercellular bridges (arrows) in metaplastic cell group in nasal smear f atrophic rhinitis Papanicolaou 940 ×*



FIG 2 — *C lls with edematous nuclei and indistinct cytoplasm in nasal smear f atroph rhinitis. Papanicolaou 940 ×*

Bacteria were abundant or very abundant in the majority of the cases. Typical was the appearance of bacteria with a thick-stemmed structure They must apparently be identified as capsulated *Klebsiella* bacteria (Fig. 22 and 27) Very few of these bacteria were found intracellularly in leukocytes.

The histochemical methods (Triple stain and acridine-orange) did not give additional information about cytological characteristics in atrophic rhinitis (cf also *Holopainen*, 1967 a)

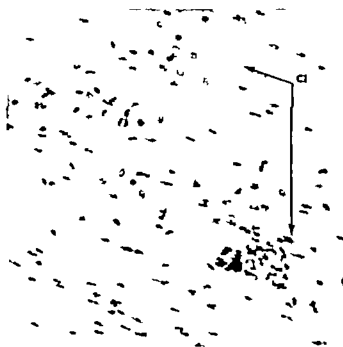


FIG 26 — *Clusters (Cl) of superficial squamous cells in nasal secretion from atrophic rhinitis Papanicolaou 190 ×*



FIG 27 — *Squamous epithelial cells (S) neutrophils (N) and thick-stemmed bacteria (B) in nasal smear of atrophic rhinitis. Acridine-orange 520 ×*

TABLE X – Cytological findings of the nasal smears of 103 patients with atrophic rhinitis expressed in per cent

Cell elements	none	few	moderate	many
Columnar epith. with or without cilia	47	29	16	8
Goblet cells	90	8	2	0
Basal cells	0	0	0	0
Squamous epith. cells	0	12	18	70
Metaplastic cells	0	9	41	50
CCP cells	69	25	5	1
Neutrophils	0	0	9	91
Eosinophils	89	9	2	0
Mast cells	99	1	0	0
Lymphocytes	15	33	54	0
Bacteria	0	9	23	68

D Discussion

In the present material only one patient could be classified as *Runge's* (1928) secondary type of atrophic rhinitis, where the etiological factor was clear. This patient had a congenital turbinal anomaly on the left side without crust formation. All the other patients belonged to the group of genuine atrophic rhinitis, where the etiological factor was called in question. The simple form of atrophic rhinitis without crust accumulation was fairly common in the present material: 29 out of 103 patients belonged to this group and the remaining 74 patients belonged to the rhinitis atrophicans foetida sive ozaena group where crust formation and foetor were predominant clinical symptoms (cf. Table VI). The simple and the foetive forms were not histologically distinguishable into two characteristic groups. In both groups the changes typical of chronic inflammation dominated the picture. Neither did the material include such cases where according to *Ruskin* (1942) and *Taylor* and *Young* (1961) the vascular changes would have been predominant, the inflammatory changes being less noticeable.

In the present material the histological finding that the epithelium was metaplastic either throughout its length or, as was more common, only partially, supports *Schönemann* (1902) and *Sarén's* (1928) findings. According to these squamous cell epithelium appears as islands of varying size in the nasal mucous membrane in atrophic rhinitis.

The histological finding of squamous cell metaplasia is not quite pathognomonic of atrophic rhinitis alone, but such metaplasia appears in other chronic inflammations and irritations in the nasal mucous membrane as well. The difference is quantitative rather than qualitative To illustrate this the b opsies from the inferior and middle turbinates of a group of patients suffering from chronic sinusitis and rhinitis were studied. Metaplastic changes were visible in the epithelium in 5—9 per cent of the cases (a detailed report will be published later) The metaplastic change in the pithelium is hardly a primary event in atrophic rhinitis, but a secondary result of prolonged irritation (bacterial toxins?) of the nasal mucous membrane. Papillomatous structure according to *Runge* (1928) characteristic of respiratory epithelium in connection with metaplastic changes, was also observed.

In the present material the connective tissue membrane was clearly differentiated from the true basement membrane. It is obvious that in earlier literature concerning nasal histopathology these two membranes were usually confused, which often makes the interpretation of results difficult. The present results do not support the view that the connective tissue membrane would thicken in atrophic rhinitis. On the contrary this membrane was thin in most of the specimens, and the true PAS-positive basement membrane was not thickened either However the basement membrane was mostly discontinuous.

The constant ppearance of mononuclear cell infiltration in the lamina propria supports the view that infection is an important factor in the development of the disease The abundance of tissue mast cells was characteristic in the present material However earlier investigations have shown (*Choleva* and *Chordes* 1898 *Sternberg* 1923 *Grahne* 1956 *Hussarek* and *Neuhold*, 1960 *Messerklinger* 1960 *Palva* and *Palva* 1962) that appearance of mast cells is not characteristic of atrophic rhinitis alone

Russel's bod es were not present, possibly owing to the fact that advanced stage of atroph c rhinitis was rare in the present material when according to the literature (*Sternberg* 1923) Russel's bod es should appear in the lamina propria of atrophied nasal mucosa.

The findings concerning the changes in the sero-mucinous glands support the earlier findings according to which the changes in the glands are not primary in atrophic rhinitis, but rather a prolonged chronic infection produces secondary degeneration of the glands, eventually causing their disappearance.

Only a few changes were found in the rteries. The present material did not show the capillary dilatations mentioned by *Taylor* and *Young* (1961)

The *histochemi ally* reacting mucin material in atrophied mucosa was clearly diminished. One reason for this was the reduction in th number of goblet cells and mucosal glands. It was d ff cult to judge whether the intensity of the react on of the single secretory element i trophied mucosa differed from that of symptomfree mucosa. The histochemical h racteristics of mucosubstances in the outer border of th epithelium nd the m cosal gl nd were mainly identical with those of the symptomfree mucosa. These result do not of course exclude possible d fferences between mucosubstances in these two gro s but further h stochem cal characterization of the mucosubst nces was not possibl w h the present methods.

There is no single histological change p thognomonic of atrophic rhinitis alone Neither is there any single element in the *cytological* smears which is ch rac teristic of atrophic rhinitis, but the composition of the cell population and the distribution f single cell elements was found t be typical of this disease For comparison th cytological picture in symptomfree nose was studied, and in addition, the cytology f approximately 200 cases of chronic alle gic and non-allergic rhinitis and chronic sinusitis was investigated (detailed results will be published later) The cellular picture of these diseases differed markedly from that of atrophic rhinitis. Table XI illustrates the differences in cell distribution in symptomfree nose chronic allergic and non allergic rhinitis as well as atrophic rhinitis.

TABLE XI — Comparison f cytological pictures f al smears i various conditio

Cell elements		Symptomfree nose (30 cases)	Chronic llergic or non-allergic rhiniti (200 cases)	Atrophic rhinitis (103 cases)
Neutrophils	number	few	mod. many	many ery ma y
	structure	distinct	distinct	partl indist nct
	phagocytizing activity	—	preserved	partly dimi ished
Eosinophil	number	none or few	none few many	none or few
Mast cells	number	none	none few mod.	none or few
Bacteria	umber	none	mod. or few	many or ery a
Columnar cells	with cilia	mod. or many	mod. or many	none or few
	without cilia	mod. or many	mod. or many	few or mod.
Goblet cells	number	moderate	mod. or many	none or few
Metaplastic cells	number	none or few	none or few	mod., many or ery a
Squamous cells	number	none or few	none or few	many or very many

Green nd *Solomon* (1962) state in their study that wl en the im munological response is bsent, the phagocytizing cti ity f the neutrophilic leukocytes is sm ll In the present material the phagocytizing activity was noted t increase when the symptoms f the disease underwent an improvement during tl treatment (*Holopa nen*, in the course f publication) The absence or great rarity of secreti eosinopl l do not support the theory of *Moritz* (1930) according to which the allergic proces th mucous membrane would be prodromal stage of the disease

As neutrophils stain blue and mast cells violet blue in *Wright* st ining method it is possible th t the numerous neutrophils might ha obscured some m st lls, but even then the mast cell were remarkably few in the cytological m teri l On the ther hand, tissue mast ll were ery bundant, and there w no correl tion between these two features

As appears from the material on symptomfree nose, the columnar cell with or without cilia was the most common cell element in the cytological samples taken by the wiping method In the cell material of common chronic rhinitis this cell element was also fairly frequent, whereas it rarely occurred in atrophic rhinitis.

The abundant number of goblet cells (more than 50 per cent of the epithelial cells) is a sign of hyperfunction of the mucous membrane This is the case in some allergic nasal affections and also in some cases of the normal material. On the other hand the goblet cells were very rare in the material of atrophic rhinitis.

According to *Bryan* and *Bryan* (1955) typical nuclear changes occur in the epithelial cells in virus infections. These viral forms of epithelial cells, which are also called CCP cells, appear abundantly in virus infections, especially during the first four or five days of the infection gradually decreasing after that. The experience of the present author agrees with those of *Bryan* and *Bryan*. On the other hand, the CCP cells are *not found in pure or primary bacterial infections* Their occurrence is also insignificant in atrophic rhinitis. Therefore it may be concluded that virus infection does not play a significant role at least in the later development of atrophic rhinitis.

The metaplasti cell can be regarded as an intermediary stage in squamous cell metaplasia (*Graham*, 1965) As was earlier mentioned, the appearance of metaplastic cells can be considered as an evidence that the cell material originated in the meta plastically changed mucous membrane as the vestibulary epithelium very seldom contains these cells. It should however be mentioned that the predominant element in the cellular mucosal material in atrophic rhinitis is the superficial squamous cell This might partly be due to the fact that these last mentioned cells exfoliate very abundantly into the secretion. Only in two or three out of 105 cases did the kera tinized anucleated squamous cells predominate which points to a very advanced metaplasia in the mucosa.

CCP = cilia cytophon

V GENERAL DISCUSSION

A Comparison of the Histological and Cytological Findings in Atrophic Rhinitis

A biopsy gives information about the state of the mucous membrane in a very limited area, whereas the cytological sample covers a wider area of the nasal cavity. An advantage of the biopsy is that it illustrates not only the epithelium, but also th deeper-lying layers of the mucous membrane. However, although the cytological sample gives direct information only bout the surface epithelium, it can also indicat the processes going on deeper down in the mucous membrane. The cytological sample cannot, of course, replace the biopsy but t is an easy tool for additional information.

On the whole ciliated columnar epithelium in the biopsy and the number f ciliated columnar cells in the smears correlated fairly well in symptomfree nose. On the other hand, ciliated cells do not often ppear in cytological samples f atrophic rhinitis, although islands of cili ted epith lium are preserved in most cases of the disease. In atrophic rhinitis squamous epithelial cells and metaplastic cells are abundantly exfoli ted in the secretion, whereas ciliated cells do not exfoliat spontaneously. It is obvious th t the ciliated epithelial cell islands in atroph ic rhinitis do not easily become the object of the wiping, as the mucous mem brane is covered with mucus and ery often also with crusts. In the present biopsy material of atrophic rhinitis columnar epithelium with r without cilia could be noted only in some specimens. In the same way most f the cyt logical specimens had no cylinder cells, and when they appeared, they were ery rare. E en more rarely had they preserved their cilia. Very few goblet cells were present in both the cytological and the histological material, which also illustrates correspondence between the results of these two methods.

When the biopsies from both the inferior and the middle turbinates conta ned squamous ep thelial metaplasia, there were ma y or ery many squamous epithelial cells or metaplastic cells in the smears f nasal secretion. It was lso clearly noticeable that the metaplasti cells were bundant i the secretion, when advanced squamous cell metaplasia occurred in the epithel um. The correlation is thus obvious betw een the occurrence of met plasia in the biopsy and the appearance of squamous epithelial and metaplastic cells in the secretion.

The inflammatory infiltration f the tissue consists mainly of lymphocytes d plasma cells, the neutrophilic leukocytes constit ting only a small part of it. The ppearance f lymphocytes in the cytological samples was common, but they were few in number. Yet there seem to be positiv correlation between the n umber of inflammatory cell in the tissue nd the ppearance of neutrophilic leukocytes in the nasal secretion. The more bundant the mononuclear cells were in the tissue the

more neutrophilic leukocytes were found in the smears of nasal secretion. Deviations from this were seen only in 5 cases out of 105

The literature contains very conflicting statements on the correlation between tissue eosinophilia and secretion eosinophilia. Some authors (*Andersen*, 1913 *Hansel* 1953 *Vahen* 1956 *Voorhorst*, 1939) think that there exists some correlation between them, whereas others (*Letcher* 1928 *Johnson* and *Goldstein* 1932) have not obtained any correlation at all. In the present material on atrophic rhinitis there were but a few cases of tissue eosinophilia and also a few cases of secretion eosinophilia, and in the smears the number of eosinophils was always small. No correlation between tissue and secretion eosinophilia was noticeable.

In some allergic manifestations of the nose *Bryan* and *Bryan* (1959 b) found an increased number of mast cells in the nasal secretion. According to them the increase in mast cells in the secretion suggests food allergy Later on *Shioda* and *Mishima* (1966) arrived at the same result in their investigations. Statements in the literature are unanimous that abundant mast cells appear in the tissue in a chronically infected mucous membrane (*Messerklinger* 1958 *Palva* and *Palva* 1962 *Hlaváček* and *Lodja* 1963) The present investigation showed that there were abundant mast cells in the nasal mucosa in atrophic rhinitis, but in no case did the secretion contain increased numbers of mast cells. Indeed in most cases the secretion lacked mast cells completely There is therefore no correlation between the mast cell contents in the tissue and in the secretion.

B Remarks on the Pathogenesis of Atrophic Rhinitis

The etiology of atrophic rhinitis is an unsolved problem. The disease is known to be disappearing from most civilized countries. According to *Saltero* (1967) the incidence of atrophic rhinitis has also decreased in Finland during the last two decades, in the last few years the morbidity has remained constant. There are several unproved hypotheses concerning the etiology of the disease based on comparative investigations of its development and morphological changes. In the literature the infection theory is one of the oldest.

The present material has not brought forward any indisputable facts concerning the etiology of the disease However the histological findings (inflammatory cell infilt ration, glandular and vascular changes) and the cytological find ngs (abundance of secretion leukocytes) as well as th bacteriological findings (abundant appearance of bacteria in the smears and in the cultures) strongly support the theory according to which a prolonged infection is on of the important factors affecting the development of the disease In every case of the material the histological picture (showing metaplasia in the nasal epithelium and degenerative changes in the stroma) and the cytological p cture of the nasal secretion (with abundant metaplastic and squamous cells in contra t to almost mplet bsence of ciliated cells) point to a long-term infection in the mucous membrane Similarly in every case of the material the bacterial culture showed t lea t one k nd of ba teria, usually various kinds (*Holopainen*

in the course of publication) *Klebsiella o enae* was by far the most common bacteriological finding, as it appeared in 70 per cent of the cases. The present study clearly shows that the infectious type of atrophic rhin tis predominates in Finland Saltero (1967) has arri ed at the sam conclusion in his investigations. It remains open why the infection shows a ery poor tendency of restitution.

VI SUMMARY AND CONCLUSIONS

Altogether 103 patients suffering from atrophic rhinitis were studied. Biopsies were taken from the inferior and middle turbinates for histological as well as histochemical investigation and smears from nasal secretion were prepared for cytological examination. 54 histological biopsies and 98 cytological samples obtained from patients without significant nasal symptoms served as a control material. In addition, 9 inferior and 8 middle turbinates were collected from autopsies for microscopic evaluation. Routine histological staining procedures were applied they included a number of stains for the demonstration of mucosubstances. Special procedures for the preparation and staining of nasal smears were employed.

The main conclusions to be drawn from the results are as follows

1 The autopsy material supports the earlier statements that the borderline between the vestibular and the respiratory epithelium varies in relation to the anterior tip of the inferior turbinate. The amount of squamous epithelium in the inferior and middle turbinates varies extensively as well.

2 The biopsy should be taken as far back as possible in order to be representative of true respiratory mucosa.

3 In the symptomfree nose the epithelium differs from what is usually regarded as normal respiratory epithelium in the literature. The pseudostratified ciliated columnar epithelium is present only in one third of the cases, whereas the stratified columnar epithelium without cilia is more common. However the squamous metaplasia is a rare appearance.

4 Nasal smears can be taken without cellular contamination from the nasal vestibule.

5. In the symptomfree nose the cellular picture of exfoliated and wiped material is quite characteristic, the columnar epithelial cells with or without cilia being the most common cell element. The goblet cells are also fairly frequent. Metaplastic and squamous epithelial cells appear only exceptionally

6 Atrophic rhinitis does not possess a pathognomonic histopathology The squamous metaplastic epithelium is, in the form of small islands in the epithelium, by far the most common alteration. In the lamina propria abundant inflammatory infiltration and numerous mast cells are common features. The connective tissue membrane and the basement membrane are not increased in thickness. Similar histological changes can be observed in the simple chronic rhinitis, but in atrophic rhinitis they are much more severe in degree and in extension. The distinction between these two diseases can thus be made in quantitative terms only

7 The histochemically demonstrable mucosubstances have no specific distribution or content in atrophic rhinitis.

8 The nasal exfoliative cytology is characteristic in atrophic rhinitis. However this

is not due to any single cell lement but to the composition of th cell population in the smears. The absence or scarcit of columnar and goblet cells is one of the typical features, as is the abund nce of neutrophils and bacteria The appe rance of a large number of metaplastic and squamous cells is characteristi of atrophic rhinitis as well.

9 Viral forms of ep thel al cells are few in cytological smears of trophic rhinitis, indicating that virus infection is not significant at least fo the later development of the disease

10 Nasal histology and exfoliati e cyt l gy correlate quite closely both in symptom free nose and in atrophic rhinitis.

11 The exfoli tive cytology is a valuable add tional tool for an early diagnosi of atrophic rhinitis.

12. Prolonged infection is likely to be the most ignif cant etiological fact r in atrophic rhinitis.

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MECHANICS OF THE HUMAN MIDDLE EAR

PRESSURE REGULATION IN AVIATION AND DIVING
A NON TRAUMATIC METHOD

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Contents

1. Basic principles in determination of middle ear mechanics

Most clinical problems relating to the function of the Eustachian tube arise from the failure of the tube to ventilate the middle ear adequately When gases are absorbed from the middle ear space, the result is that the intratympanic pressure gradually becomes lower than the extratympanic. Therefore determinations of the middle ear pressure will indirectly provide information on dysfunction of the Eustachian tube. Such determinations are of great clinical importance and some of the methods are widely used.

The methods for pressure determination in the middle ear are commonly divided into direct and indirect ones. For the determination direct methods need a free air contact between a manometer system and the air-filled middle ear space This contact is produced by puncturing either the tympanic membrane or the mastoid process in man or the bulla of animals. Other methods, however which do not need any surgical intervention are more commonly used on man. With such methods the middle ear pressure behind the intact tympanic membrane can be estimated provided that the drum is movable.

The present authors are specially interested in a further development of indirect methods for determinations of middle ear mechanics. These methods are based on recordings of the movements of the tympanic membrane. The aim is to show that such measurements performed during the conditions defined, give possibilities to determine the volume of the air-filled ear space, the elastic properties of the tympanic membrane, and events during changing ambient pressure or during the act of opening the Eustachian tube. A great many problems concerning the mechanics of the middle ear can be solved in man not only during ordinary conditions but also during special man-made conditions such as aviation and diving.

In many aviation and naval medicine centers the selection of personnel with normal function of the Eustachian tube suitable for aviation, submarine activity diving and working in caisson is performed during pressure chamber "flights The candidates are here trained to equilibrate the middle ear pressure to rapidly changing ambient pressure simulating those occurring during flight and diving. This testing and screening is very important and many cases of aero-otitis media can be prevented in this way During the investigations the subjects have to mention any aural discomfort and after each pressure test the tympanic membranes are inspected by otoscopy During the testings some of the candidates, however are found to be unable to equilibrate the pressure in the middle ear even after instruction, and must be dismissed.

In 1950 the degree of aural barotrauma resulting from recompression and decompression was studied by Chang, Margaria and Gelfan on monkeys

exposed to ambient pressure changes in a pressure chamber. In most of the experiments the animals were under anaesthesia but a few unanaesthetized monkeys were also used. As a routine procedure the *tympanic membranes had to be punctured* prior to the experiments. Thus the middle ear cavity and the external ear canal communicated. Then the external canal was airtightly connected to an electric manometer. In this way the pressure changes in the middle ear could be directly measured during the flights and taken as an expression of the ventilatory function of the Eustachian tube during decompression and recompression.

Hitherto however no objective method has been reported by which the ability of the Eustachian tube to equilibrate the middle ear pressure can be determined simultaneously with the pressure change exposition in the pressure chamber in subjects with an intact ear drum. The present authors believe that if such a principle of determination could be used *during* the flights the pressure regulatory function of the Eustachian tube could be more completely evaluated. Furthermore in cases with disturbed function a diagnosis could be obtained and in some cases probably individual instructions for making more effective equilibration manoeuvres could be given.

EARLIER METHODS USED

The following account is mainly concerned with methods applicable only in cases with intact tympanic membrane i.e. methods used for direct and indirect determinations of the middle ear pressure. Furthermore earlier methods will be reported by which the volume displacement of the tympanic membrane has been determined *quantitatively*.

DETERMINATION OF THE MIDDLE EAR PRESSURE

Direct methods

In 1954 Link and Handl studied the pressure changes in the middle ear on *guinea pigs after puncturing the bulla*.

Direct pressure measurements on man in cases with intact tympanic membranes have been performed by Flisberg, Ingelstedt and Örtegren in 1963. By puncture of the mastoid process a direct communication with the air-filled ear space was effected. Ingelstedt and Jonson (1966) used the same puncture technique. For natural reasons only few direct determinations of the middle ear pressure have been performed on man.

Indirect methods

The first methods of clinical importance were described by Krassnig (1935) and Zollner (1942). Equilibration of the pressures on both sides of the tympanic membrane was produced by creating a pressure change in the external ear canal thereby allowing the membrane to move to its "neutral position". This state was determined by inspection and the pressure needed outside the drum was simultaneously determined.

This state of equilibration has later been determined by a pure tone which is sent into the auditory canal, i.e. the pneumophone method. The pressure in the canal is varied until the subjects point out the maximum loudness of the tone sent in (van Dishoeck, 1937) By pressure chamber experiments on man, Perlman (1943) demonstrated that accurate information on the pressure across the drum could be obtained with the pneumophone

The acoustic impedance method was devised for clinical use by Metz (1946) Thomsen (1955) measured changes in the impedance of the tympanic membrane as an indication of changes in the middle ear pressure caused by tubal air passage. In 1957 Thomsen used the same technique in connection with pressure changes in the auditory canal brought about in a pressure chamber If for example a person has originally a negative pressure in his middle ear cavity the absorption of sound entering the external ear canal will rise as long as the pressure in the chamber decreases down to the pressure level prevailing in the middle ear

Comments

Unfortunately neither Perlman s nor Thomsen s techniques admit of measurements simultaneous with the ambient pressure changes. Point values only can be determined at constant levels of the ambient pressure in the chamber Both authors have performed control experiments in the pressure chamber for evaluation of the validity of the methods used. So for example both of them show the validity of the pressure determination when a subject is exposed to an ambient pressure change of +5 cm H_2O while he is instructed not to swallow If the pressure in the external ear canal is changed, the indication techniques show optima when this pressure reaches the original pressure at which the tympanic membrane should be in its neutral position. These results show that the pneumophone and impedance methods allow determinations of the pressure applied to the external ear canal which will equilibrate the pressure across the drum. However this pressure is not the same as the original pressure existing in the middle ear prior to the procedure of the determination, because the uncontrolled volume displacement of the ear drum influences the original middle ear pressure according to Boyle s law This was earlier discussed by Flisberg, Ingelstedt and Örtegren (1963) and will further be evaluated in chapter 3

METHODS FOR DETERMINATION OF THE VOLUME DISPLACEMENT OF THE EAR DRUM

The volume displacement of the tympanic membrane when caused by known pressure changes applied to the middle ear has been studied by Flisberg, Ingelstedt and Örtegren (1963) The calculations were based on closed manometry in the external ear canal simultaneous with direct pressure recordings from the middle ear space The same technique of closed manometry was performed on a large material of patients by Riu Flottes, Bouche Le Den (1966)

Comments

Closed manometry is not always suitable for the determination of the volume displacement of the tympanic membrane, for reasons that will be discussed in chapter 7 Therefore a new improved technique was presented by Ingelstedt and Jonson (1966) and is below described in detail

From the present ENT clinic several studies on the mechanics of the middle ear have been presented (Flisberg, Ingelstedt and Ortegren 1963 Ingelstedt 1964 Flisberg 1966 Ingelstedt and Jonson 1966) To obtain a complete picture of the function of the middle ear it was earlier necessary to achieve a direct contact with the middle ear cavity One purpose of the present investigations is to show how many mechanical properties of the middle ear can be studied without direct contact with the middle ear via a puncture of the tympanic membrane or the cell system of the mastoid process. However a prerequisite for some of the methods used in the present investigations is ability on the part of the subject to equilibrate the pressure in the middle ear cavity with the pressure in the rhinopharynx by opening the Eustachian tube. This limits the possibilities of using the present methods in cases with severe dysfunction of the Eustachian tube. Such dysfunction is however easily recognized. The present methods provide great possibilities of studying the physiology of the middle ear system in normal man and the ability to keep the pressure in the middle ear at about ambient pressure. The latter ability is of particular importance in aviation and diving and can be studied during rapid changes of ambient pressure

SYMBOLS

Patm	atmospheric pressure on the ground.
Pm	middle ear pressure.
Pm_d	the middle ear pressure minus the pressure of saturated water vapor at 37 C, this being regarded as noncompressible in connection with Boyle's law
Pm	the middle ear pressure related to the changing ambient pressure (Pm = Ptm)
Pec	the pressure in the external ear canal.
Ptm	Pm–Pec i.e. the pressure across the tympanic membrane
Pv	the transmural pressure of the vessels in the mucosa of the middle ear i.e. the pressure within the vessels related to the pressure outside the vessels.
Prh	the pressure in the rhinopharynx.
Pch	the pressure in the pressure chamber
Vm	the volume of gas enclosed in the air space of the ear in the text often referred to as the ear space
ΔV_{tm}	the volume displacement of the tympanic membrane.
ΔV_t	the volume of a gas portion passing the Eustachian tube when the tube opens.
ΔV_{diff}	the gas volume leaving the middle ear cavity and entering the blood by diffusion.
ΔV_{muc}	the volume changes of the mucosa lining the ear space.
ΔV	the air volume passing through the resistor of the flow meter
$\dot{V}_{tm}$	instantaneous volume flow rate in the ear canal caused by movement of the tympanic membrane
$\dot{V}_r$	the instantaneous volume flow rate through the flowmeter

Pressures except Pm, are given relative to the atmospheric pressure on the ground.

Δ placed before a symbol means a change in this variable.

Signs of the volume changes appear from Fig. 1

Pressures are expressed in cm H_2O volumes in microliters (μl) volume flow rates in microliters/sec ($\mu l/s$)

THE MIDDLE EAR SYSTEM

In studies on the mechanical properties of the middle ear it is highly convenient to start from a unified model as shown in Fig. 1 In this model the middle ear cavity consists of the tympanic cavity and the air-filled cell system in the mastoid process in connection with the tympanic cavity This air-filled cavity is regarded as a rigid chamber lined with a thin mucosa. The cavity is intermittently open to the atmosphere via the Eustachian tube thus admitting gas portions to pass to or from the rhinopharynx. In the external ear canal the middle ear cavity is separated from the atmosphere by the tympanic membrane. The tympanic membrane is connected to malleus, incus and stapes and via these to the musculus stapedius and the musculus tensor tympani. By the elastic properties of the tympanic membrane below is really meant the elastic properties of this whole mechanical system.

For different reasons the gas volume in the middle ear cavity may from a certain moment, undergo expansion or compression amounting to ΔVm (expansion i.e. $\Delta Vm > 0$) (See Fig 1)

1 Gas portions enter or leave via the Eustachian tube, ΔVt.
2. The tympanic membrane moves outwards or inwards, ΔVtm.
3. *Gas enters the blood from the cavity via diffusion, ΔVdiff*
4 The volume of the mucosa lining the middle ear cavity may change ΔVmuc.

$$\Delta Vm = +\Delta Vdiff - \Delta Vmuc + \Delta Vtm - \Delta Vt \qquad \text{eq. 1}$$

As volume changes caused by diffusion are slow it is possible to omit the ΔVdiff in studies on rapid events i.e. for most purposes events lasting less than 0.5 min. (Ingelstedt and Jonson, 1966 see also chapter 7) In such cases

$$\Delta Vm = -\Delta Vmuc + \Delta Vtm - \Delta Vt \qquad \text{eq 2}$$

Volume changes of the mucosa ΔVmuc, take place during development of for example oedema, also including development of transudate. Such changes are slow Rapid changes of the mucosa take place when the pressure in the middle ear cavity changes, or when the capillary venous pressure in the mucosa changes. Such volume changes are however small see chapter 2. Therefore ΔVmuc may in many cases be disregarded. In such cases

$$\Delta Vm = \Delta Vtm - \Delta Vt \qquad \text{eq 3}$$

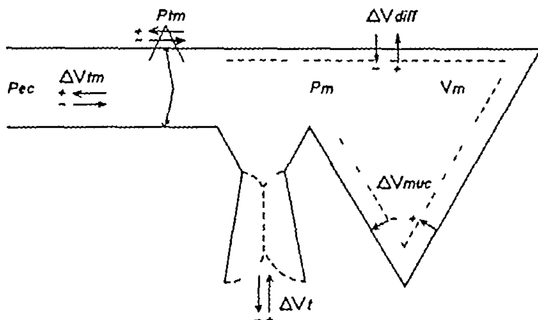


Fig. 1 The middle ear model.

Under some conditions the Eustachian tube remains closed during the time when ΔVm is observed.

Then

$$\Delta Vm = \Delta Vtm \qquad \text{eq 4}$$

if the approximations above are still permitted.

The pressure in the external ear canal Pec, acts on the tympanic membrane from the outside. The pressure in the middle ear Pm, acts from the inside of the drum.

The pressure across the tympanic membrane, Ptm, is defined by the equation

$$Ptm = Pm - Pec \qquad \text{eq 5}$$

When $Ptm = 0$ the tympanic membrane is said to be in its neutral position.

PRESSURE–VOLUME RELATIONSHIPS IN THE MIDDLE EAR

Boyle's law may be applied to the gas volume in the middle ear cavity. As water vapour is regarded as non-compressible

$$Vm \cdot Pm_0 = (Vm + \Delta Vm) \cdot (Pm_0 + \Delta Pm_0) \qquad \text{eq 6}$$

As long as ΔPm_1 is very small compared to Pm_1 clearing and solving give

$$\Delta Vm = -\Delta Pm_1 \frac{Vm}{Pm_1} \qquad \text{eq 7}$$

A combination of equation 7 and equation 3 gives

$$\Delta Vt - \Delta Vtm = \Delta Pm_1 \frac{Vm}{Pm_1} \qquad \text{eq. 8}$$

Equation 8 describes the pressure volume events in the middle ear cavity under circumstances discussed at equation 3

The relationship between ΔPtm and ΔVtm, i.e. the pressure volume events taking place across the tympanic membrane cannot be described in an analogous way as this relationship is alinear and not easily described in a mathematical form. This relationship

$$\Delta Ptm = f(\Delta Vtm)$$

can be described by a diagram after a study performed on every single subject. Such a study is of central importance in the present investigations as the pressure volume properties of the tympanic membrane interfere with all phenomena studied and discussed.

In the present investigations we have disregarded the inertia of the components of the model, as we are dealing with slow phenomena.

METHODS

Pressure chamber

A pressure chamber made of reinforced concrete, internal volume 23 m³ was built up at the ENT-department. Via a pipe system the chamber was connected to a high pressure fan by which air could be blown into or evacuated from the chamber yielding pressure variations within the range of ±50 cm H_2O (Fig. 2).

With the aid of a special valve system in the pipes an underpressure of −50 cm H_2O in the chamber could be changed over to an overpressure of 50 cm H_2O within 25 sec. This pressure could be turned back again to −50 cm H_2O in further 25 sec.

The investigations were performed in this chamber which contained the subject, the investigator and all electronic device during all the pressure change tests

Prof. C. Allander of Kungl. Tekniska Högskolan and the staff of AB Svenska Fläktfabriken have taken part in the construction of the chamber. This construction has been made possible thanks to financial support from Malmöhus läns landsting and AB Svenska Fläktfabriken.

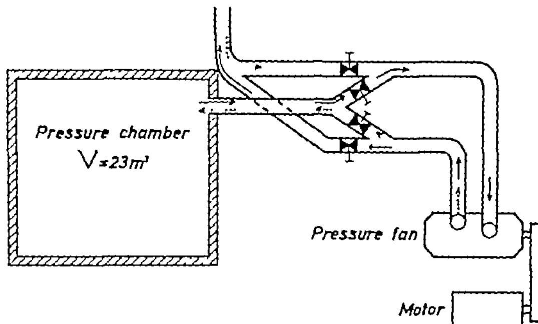


Fig. 2. Pressure chamber arrangements.

EQUIPMENT FOR DETERMINATION OF VOLUME DISPLACEMENT IN THE EXTERNAL EAR CANAL, CAUSED BY MOVEMENTS OF THE TYMPANIC MEMBRANE

Determinations of movements of the tympanic membrane are the basis from which all other mechanical properties of the middle ear are deduced. The device for such determinations is composed of different parts (Fig 3)

A catheter with a rubber disc is airtightly inserted into the inner bony part of the external ear canal.

A flowmeter is connected to the above-mentioned catheter The flowmeter is a pneumotachograph consisting of a single capillary resistor across which the pressure drop is measured by a differential gas pressure transducer (EMT 32, AB Elema-Schönander Stockholm) The differential pressure acts upon a membrane giving mechanical deviations. The deviations are measured capacitively and the output of the transducer is transformed into a dc-signal which is proportional to the differential pressure acting upon the membrane

Thermostat For minimizing the thermal zero-line drift of the transducer this has been mounted into an airtight, thermostated metal container at a constant temperature of 18 C ± 0 01 C The airtightness prevents any pressure change during the experiments on the outside of the transducer This is necessary for avoiding influence of temperature changes on the transducer at compression and decompression of the ambient air

Amplifiers. The signal from the differential pressure transducer is amplified. Special arrangements are made for proper adjustment of zeroline drift.

Integrator circuit The amplified flow signal is integrated with respect to time giving volume changes When the output from the integrator has reached

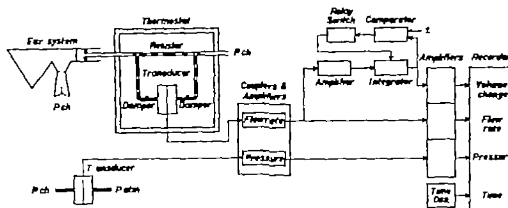


Fig. 3. Block diagram of the equipment for pressure flow and volume determinations.

a certain magnitude the condensator of the integrator may be automatically short-circuited and the integration starts again from the zero-line.

The pressure changes in the pressure chamber are recorded via a separate transducer

Recorder The flow pressure and volume signals are amplified and recorded on a multi-channel Mingograph (Mingograph 81 AB Elema-Schönander Stockholm)

DATA AND SPECIFICATIONS OF THE EQUIPMENT

Pneumotachograph capillary = resistor

The resistor has a resistance of 0 045 mm H_2O/microliter per sec. The pressure-flow relationship is linear within a flow velocity range of 0–500 microliters/sec (Fig. 4)

Properties of the differential gas pressure transducer

Pressure range ± 22.5 mm H_2O

Linearity better than 2 % within the pressure range.

Hysteresis less than 0 1 % of the pressure measured.

Thermal zero deviation 0 0375 mm H_2O centigrade.

Dynamic sinusoidal response flat over 0–22.5 cps.

Dynamic sinusoidal differential balance, i e. symmetry of the two sides of the differential pressure transducer: less than 1 % error over 0–22.5 cps.

Properties of the complete flow and volume measuring unit

Sinusoidal frequency response flat over 0–11 cps. For this testing a syringe graded in microliters, is used as an engine-driven piston pump Each stroke discharges a constant volume of air which is sucked or blown through the flowmeter at varied frequencies. As appears from Fig. 4 the volume discharge is correctly recorded up to 11 cps.

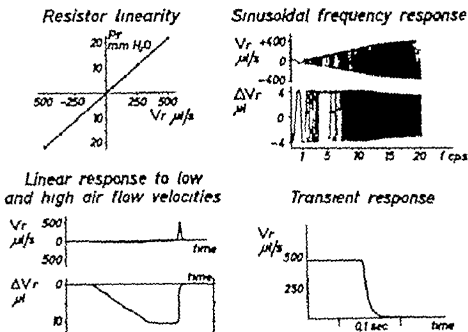


Fig. 4 Characteristics of the flow-volume device

Transient response 95 % response in 15 msec, (Fig. 4) This testing is performed with the aid of a glass syringe connected to the ear tubing system. When the syringe is held vertically the highly movable piston is allowed to fall against the bottom of the syringe. The response is recorded from this moment, when the flow is abruptly interrupted.

The linear response to low and high air flow velocities 0–500 microliters per sec This response is produced with the aid of a syringe graded in microliters A constant volume of air is sucked or blown through the system at varied flow velocities As long as the air flow response is linear the recorded air volume is constant—see Fig 4

Linearity of the recorded deflections 1 % error within ± 40 mm recorded deflection.

The zero drift ± 0.25 microliters/min

Calibration accuracy 1 microliter ± 5 % Calibration is made before and after each experiment with the aid of a syringe graded in microliters.

PROCEDURE

The subject is sitting up comfortably in a chair the head propped by the backrest but no special head-rest is used. The chair is so constructed that the position of the subject can be changed during the investigation from sitting upright to lying down in a recumbent dorsal position. First the inner bony part of the external auditory canal is airtightly connected to the air flow and

volume measuring device via a tubing system. Around the aural end of the catheter a circular rubber disc of 3 mm thickness is mounted. The diameter of this disc must be individually so adjusted that it completely occludes the lumen of the ear canal, thereby preventing any sliding of the disc along the walls of the canal. The disc is introduced without any application of local anaesthesia. The procedure is not particulary uncomfortable for the subjects. In order further to secure that the connection to the canal is perfectly airtight, some high vacuum grease is applied on the outside of the disc. No disturbances must be recorded if the subject opens his mouth or makes other movements of the mandibular joint. *If this should happen, the disc is incorrectly placed* in the movable outer part of the external ear canal. This entire procedure must be carried out with the greatest care, so that reliable recordings of the drum movements can be obtained during different experimental procedures. In some cases however the anatomical configuration causes difficulties or even makes impossible correct fixing in the bony ear canal of the present cuff

SUMMARY

A unified model of the middle ear is described. A method has been devised for registration of the volume displacements of the tympanic membrane caused by changing pressure across the membrane. When the membrane is moving an air flow is produced in the external ear canal. This flow is recorded by a flowmeter connected to the canal. The flow signal is integrated with respect to time thus providing information on the volume displacements. Small volume displacements can be recorded with high accuracy (1 microliter ±5 %)

2. Effect of the middle ear pressure on the aural mucosa volume

As discussed above, changes in the mucosa volume of the middle ear may be of importance for the middle ear mechanics Changes in Pm cause a change in the transmural pressure of the vessels in the mucosa lining the middle ear cavity This results in a volume change of these vessels owing to their elasticity The volume change mainly affects the capillaries and the veins because of the greater elasticity of those vessels compared to the elasticity of the arteries. Changes in the rate of extravasation of fluid are supposed to be too slow to interfere with the present problems. When the gas volume in the middle ear is expanded by an underpressure the ΔVmuc will contribute with an unknown volume change (equation 2) The influence of this factor on the present studies is analyzed below

METHOD

Changes in Pm cause changes in the transmural pressure of the vessels in the mucosa (Pv) resulting in changes in mucosa volume (ΔVmuc) This ΔVmuc cannot be separated from the concomitant volume changes caused by expansion or compression of the middle ear gas. In order to produce changes in Pv without changing the volume of the middle ear gas the capillary venous transmural pressure was changed by changing the intravascular pressure, which was produced by manual compression of the veins on the neck or by changes in posture from the supine to the sitting position. The resulting change in the venous pressure was determined via a catheter (Cournand no 7) placed in the bulb of the jugular vein about 2 cm caudally to the external auditory canal introduced via a cubital vein according to a technique by Lindell, Nilsson, Roos and Westling (1962) If no perforation of the tympanic membrane was present a small incision was made. The flowmeter was connected to the external ear canal.

The pressure changes in the bulb of the jugular vein were recorded simultaneously with the resulting volume displacements in the external ear canal, reflecting changes in the mucosa volume ΔVmuc. It is supposed that changes in the venous pressure in the bulb of the jugular vein cause corresponding transmural pressure changes in the capillary venous system in the middle ear mucosa. Thus the relationship between changes in the transmural pressure of the veins and capillaries and the volume changes of the mucosa in the middle ear can be studied.

SUBJECTS

Four subjects were examined. Two of them were healthy volunteers without any history of ear disease. Two subjects had chronic otitis with large central perforations of the tympanic membrane.

RESULTS

A sample recording is shown in Fig. 5. This figure shows that after rise of the venous pressure (ΔPv) there is a rapid increase of the volume of the mucosa ($\Delta Vmuc$) resulting in a recorded volume displacement. Fig. 6 shows the relationship between the recorded $\Delta Vmuc$ and ΔPv in subject 2. Three of the four subjects showed such a slightly alinear relationship. In the fourth subject too few points were obtained to assess possible alinearity.

Table I.

Subject	Diagnosis	$\Delta Vmuc/\Delta Pv$ (µl/cm H_2O)	Vm (µl)
1	otitis med. chron.	0.53	8000
2	otitis med. chron.	0.44	5400
3	normal	0.43	
4	normal	0.29	
	mean	0.42	

Table 1 shows that the mean change of the mucosa volume was 0.42 l/cm H_2O (range 0.29–0.53) when determined within the ΔPv range of 0–10 cm H_2O.

DISCUSSION

The gas in the middle ear Vm, is expanded by a ΔVm when an underpressure ΔPm_4 is applied. Boyle's law gives

$$\Delta Vm = -\frac{Vm \ \Delta Pm_4}{Pm_4}$$

If Vm ranges between 2000 and 10000 microliters $\frac{\Delta Vm}{\Delta Pm_4}$ ranges between 2 and 10 microliters/cm H_2O. But the mucosa expands by the $\Delta Vmuc$ when underpressure is applied. According to our results this expansion is about 0.4 microliters/cm H_2O. If $\Delta Vmuc$ is disregarded, i.e. the middle ear is considered to be a rigid chamber then this $\Delta Vmuc$ will be regarded as part of the expansion of the middle ear gas. This results in an erroneous determination of Vm.

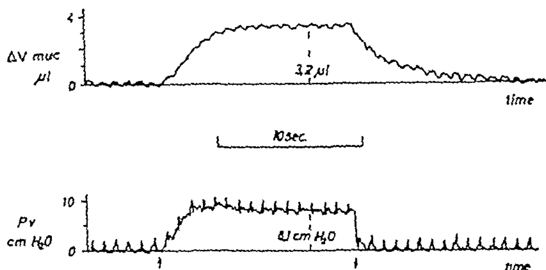


Fig. 5 Original tracing of changing venous pressure (Pv) and of the resulting volume change of the aural mucosa, (ΔVmuc) in subject 2.

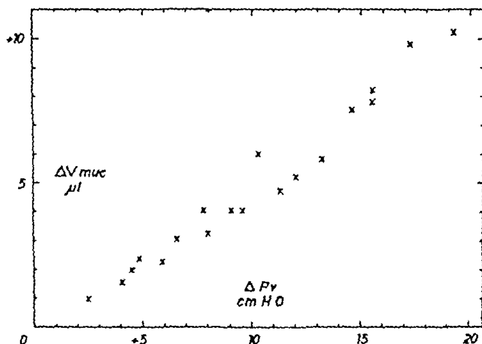


Fig. 6 Relationship between the changes of venous pressure and of the aural mucosa volume in subject 2

If $\frac{\delta Vmuc}{\delta Pm}$ is supposed to be 0.4 and $\frac{\delta Vm}{\delta Pm} = 10 - 2$ microliters/cm H_2O the error will range between $\frac{0.4}{10}$ 100 and $\frac{0.4}{2}$ 100 i.e. 4 – 20 %

The above shows that the volume changes of the mucosa caused by changing pressure in the middle ear may be of considerable importance in small ear spaces. In a system of about 6 ml as is the case in the subjects presented in the following chapters the error in the Vm-determination would be $\frac{0.42}{6} \cdot 100$ i.e. 7 %. This error has been considered acceptable and no correction has been performed.

The error caused by omitting ΔVmuc is also of some importance in the determination of other phenomena as for example tubal ventilation. In some experiments Pm is rather much higher than 10 cm H_2O. In some instances the ΔPv/ΔVmuc diagram showed a steeper rise at high pressures and the error will therefore be correspondingly greater in calculation of for example ΔVt. In the present investigations however the error introduced by omitting ΔVmuc seems to be less than 10 %. But if ΔVmuc/ΔPv could be determined on ear cases with more intense congestion of the mucosa i.e. at acute otitis media, bigger volume changes might have been recorded as a result of the intense vascular dilatation in the mucosa.

The results are obtained at venous pressures ranging from about 0 to +20–30 mm Hg, which is supposed to correspond to the transmural venous pressure. With the present method no data can be obtained at negative trans mural pressure corresponding to positive middle ear pressures. It is reasonable to suppose that the capacitance vessels are compressed under such conditions and small mucosa volume changes occur at different negative transmural venous pressures.

SUMMARY

In studies of the mechanical properties of the middle ear the ear space is often regarded as a rigid chamber. However changing pressure in the middle ear affects the volume of the vessels in the mucosa lining the ear space. Such volume changes that have previously been neglected introduce errors in the variables to be studied. Therefore the relationship between changes in the transmural pressure in the mucosal vessels and volume changes of the mucosa has been studied in four subjects. The results obtained at experimental conditions similar to those used in chapters 3 to 6 show that the volume changes of the aural mucosa are relatively small and this error is therefore negligible in the determination of the actual aural phenomena in normal subjects

3 The effect of changing ambient pressure on the middle ear Determination of the elastic properties of the tympanic membrane and the volume of the air-filled middle ear system

Changes in the pressure in the external ear canal cause a change in the pressure gradient across the tympanic membrane, which undergoes a corresponding volume displacement, ΔVtm. ΔVtm then equals a ΔVm (eq 4) ΔVm corresponds to a pressure change ΔPm, according to equation 7 According to equation 5 the pressure changes will be

$$\Delta Pec = \Delta Pm - \Delta Ptm \qquad \text{eq 9}$$

i e the changes in ambient pressure ΔPec will be distributed between a change in the middle ear pressure and the pressure across the tympanic membrane. Combining equation 9 with equation 7

$$\Delta Pec = -\frac{Pm_1 \ \Delta Vtm}{Vm} - \Delta Ptm \qquad \text{eq 10}$$

Equation 10 tells us that the distribution of a change in the ambient pressure is affected by 1) the original ambient pressure, 2) the volume of the middle ear system and 3) the elastic properties of the tympanic membrane. These factors thus determine the volume displacement and the pressure changes across the membrane and within the middle ear which result from a change in the ambient pressure. In the following account it will be shown how the effect of changing ambient pressure may be studied in terms of

$$\Delta Pec = f\,(\Delta Vtm)$$

and

$$\Delta Ptm = f\,(\Delta Vtm)$$

THE PRESSURE VOLUME RELATIONSHIP OF THE COMPLETE MIDDLE EAR SYSTEM STUDIED AS VOLUME DISPLACEMENT OF THE TYMPANIC MEMBRANE AT CHANGING EXTERNAL EAR CANAL PRESSURE

i e

$$\Delta Pec = f\,(\Delta Vtm)$$

Procedure illustrated in Fig 7 a to c. Originally the membrane is in a neutral position with atmospheric pressure on both sides. Then the pressure in the chamber and the external ear canal is increased to +5 cm H_2O i.e $\Delta Pec = 5$. The ear drum moves inwards producing a ΔVtm_1 However the volume re-

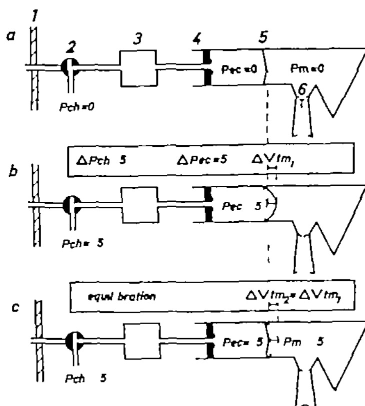


Fig. 7 Procedure for determination of ΔPec = f (ΔVtm) 1 Wall of pressure chamber 2. Stop-cock, 3. Flow volume device, 4 Rubber disc 5. Tympanic membrane 6. Aural end of the Eustachian tube.

corded by the flowmeter (ΔVr) is not equal to ΔVtm_1 since there is a simultaneous compression of the gas in the external ear canal In the transition from Fig. 7 b to c subject equilibrates the pressure across the tympanic membrane. The membrane springs back to its neutral position producing a ΔVtm_2, which is recorded accurately by the flowmeter It is obvious that $\Delta Vtm_1 = -\Delta Vtm_2$ We have thus determined the ΔVtm corresponding to a known ΔPec. The manoeuvre is repeated at different ΔPec, and the data are plotted in a diagram (Fig. 9 a) describing ΔPec = f (ΔVtm)

THE ELASTIC PROPERTIES OF THE TYMPANIC MEMBRANE STUDIED AS ITS PRESSURE VOLUME RELATIONSHIP

i.e.

$$\Delta Ptm = f\ (\Delta Vtm)$$

Procedure illustrated in Fig. 8 a to c. The subject swallows to equilibrate the Pm when Patm prevails in the ear canal and in the pressure chamber (not

shown in figure) The external ear canal is connected to the atmosphere outside the pressure chamber and the pressure in the chamber is changed to for example +5 cm H_2O resulting in the situation in Figure 8 a The subject then equilibrates his Pm to chamber pressure, producing a ΔPm that equals +5 and a ΔVtm_3 which is recorded. The chamber pressure is then lowered to zero and the subject equilibrates again, producing a recorded ΔVtm_4 (Fig. 8 b to c) when the tympanic membrane returns to its neutral position The ΔVtm_4 recorded at this second manœuvre was not significantly different from the one recorded at the first manœuvre (ΔVtm_3) when the tympanic membrane moved from its neutral position. Thus we know ΔPm = ΔPtm at the moments of equilibration when the corresponding ΔVtm is recorded. The manœuvre is repeated at different chamber pressures yielding data in the pressure-volume diagram of the tympanic membrane (Fig. 9 b) which describes ΔPtm = f (ΔVtm)

RESULTS

The data in Figure 9 can be used together with equation 7 to examine the mechanical properties of the middle ear and the events at changing ambient pressure

Assume that the ambient pressure changes from 0 to −5 cm H_2O In Fig 9 a the corresponding ΔVtm is read to be 8 microliters In Fig 9 b the ΔPtm corresponding to a ΔVtm of 8 μl is read to be 3 8 cm H_2O Thus we get
From equation 9

$$-5 = \Delta Pm - 3.8$$
$$\Delta Pm = -1.2$$

From equation 7

$$8 = +1.2 \frac{Vm}{960}$$
$$Vm = 6400 \text{ microliters.}$$

ΔPec = −5 cm H_2O
ΔVtm = 8 microliters
ΔPtm = 3.8 cm H_2O
ΔVm = 8 microliters
ΔPm = −1.2 cm H_2O
Vm = 6400 microliters

The information presented in Figure 9 thus yields information not only on the elastic properties of the tympanic membrane (Fig 9 b) or the elastic properties of the complete middle ear system (Fig. 9 a) but on the volume of this system

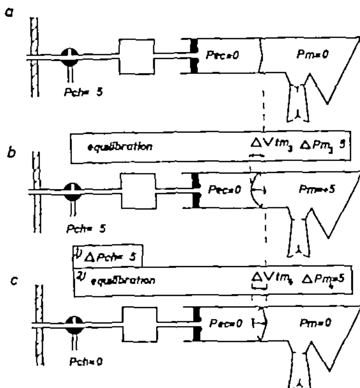


Fig. 8. Procedure for determination of ΔPtm = f (ΔVtm)

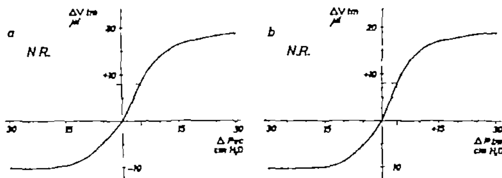


Fig. 9 a. Relationship between the changing external ear canal pressure and the volume displacements of the tympanic membrane ΔPec = f (ΔVtm)
Fig. 9 b. The elastic properties of the tympanic membrane, ΔPtm = f (ΔVtm)

as well. Furthermore it provides possibilities to predict what will happen to the different variables when the pressure in the external ear canal changes.

Fig. 9 permits calculation of changes in an original pressure in the middle ear when the pressure in the external ear canal is changed as by the pneumophone method.

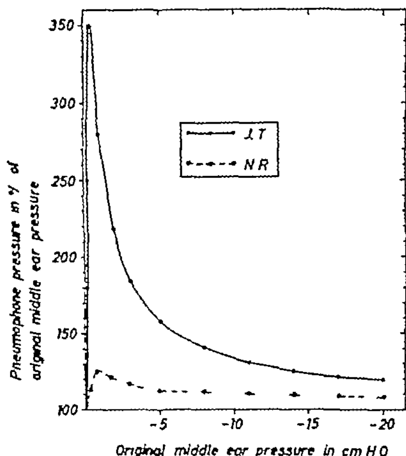


Fig. 10 Prediction of the pneumophone pressure related to the original middle ear pressure in two subjects.

Fig. 10 shows a predicted comparison between the original middle ear pressure and the pressure applied to the external ear canal which will equilibrate the pressure over the tympanic membrane, i.e. the pneumophone pressure on two subjects J.T. with an abnormal ear drum and N.R. with a normal ear drum (for the data of both cases see chapter 5 and Fig. 16 a and b). From Fig. 10 it appears that if case J.T. with a flaccid tympanic membrane had an original middle ear pressure of −5 cm H_2O this negative pressure is increased by the pneumophone procedure with about 60 %. In the normal ear case N.R., however, the same original intratympanic pressure is increased only about 10 % by the procedure.

HYSTERESIS OF THE PRESSURE VOLUME RELATIONSHIP OF THE TYMPANIC MEMBRANE

The data on the pressure volume relationship of the tympanic membrane are obtained under static conditions, i.e. the volume displacement is determined when the drum moves from one static position to another, one of them being equal to the neutral position of the tympanic membrane. It could not be taken

for granted that the tympanic membrane would follow the same pressure volume relationship during inflation, i.e. moving from its neutral position, as during deflation, i.e. moving towards its neutral position.

It might further be possible that a special pressure volume relationship exists under dynamic conditions, i.e. during a movement of the tympanic membrane. These possibilities are here discussed in terms of hysteresis of the tympanic membrane. It should be emphasized that we are concerned with slow events, so that hysteresis depending on inertia of the ear drum system is not to be expected.

No hysteresis could be observed in the experiments on the pressure volume relationship described above, where determination were made under static conditions during both inflation and deflation.

Special problems are connected with studies on dynamic hysteresis of the tympanic membrane. Instantaneous and simultaneous data of ΔPtm and ΔVtm must be recorded under dynamic conditions. The pressure in the external ear canal must be constant to allow accurate determination of ΔVtm. Thus Pm must vary Pressure variations can be transmitted to the middle ear via a route allowing free gas contact with the middle ear i.e. a puncture or patulous tube. However ΔPm equaling ΔPtm cannot be determined by this same route under dynamic conditions as pressure drops within this route will result from air flowing through it. This would cause a phase lag and a damping of the pressure within the middle ear compared to the pressure measured. This would simulate hysteresis of the tympanic membrane Therefore Pm must be determined via a second route to the middle ear Subjects with a patulous tube offer a possibility for such a study Pm may be measured via a puncture of the mastoid cell system at the same time as pressure variations in the rhinopharynx are transmitted to the middle ear via the patulous tube Simultaneously ΔVtm may be measured via the external ear canal.

In connection with another examination we have had an opportunity to perform such a study in one case. Pressure variations in the nasal cavity were obtained by letting the subject breathe through one nostril narrowed by slight external compression. The pressure in the rhinopharynx, Prh, was determined via a tube completely blocking the second nostril. Pm was determined via a puncture of the mastoid cell system. Fig. 11 shows the result. The Pm variations are out of phase and damped as compared to the Prh variations at ordinary respiratory frequencies. The ΔVtm variations and the Pm = Ptm variations are in phase. If plotted in a two-dimensional diagram (Fig 11) no hysteresis can be observed, all data are grouped closely around one line.

COMMENTS

To a great extent the pressure volume diagram of the tympanic membrane influences the events taking place at changing ambient pressure or at resorption of gases from the middle ear acting like a pressure regulator It also provides

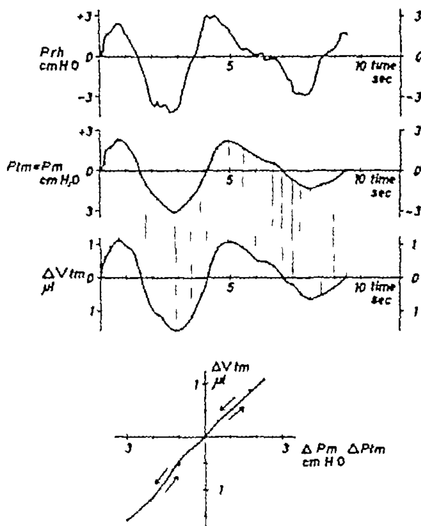


Fig. 11 Dynamic pressure-volume relationship of the tympanic membrane in a patulous tube case. Original tracings and the resulting pressure-volume diagram.

an elastic force promoting gas passage through the Eustachian tube at moments of tubal opening.

Any hysteresis of the pressure volume relationship of the tympanic membrane would affect these events, possibly with significant physiological importance. Hysteresis could result from a changing tension of the musculus tensor tympani at deflation, respectively inflation or from rearrangement of elastic fibres of the tympanic membrane.

In the present investigations no hysteresis of the pressure volume-diagram of the tympanic membrane could be observed either when determined under static conditions (4 cases) or when determined under dynamic conditions (one case). The present authors have therefore regarded the pressure volume relationship of the tympanic membrane as a fixed relationship determined as described above.

Further studies on these problems performed over a greater pressure range and over a greater frequency range would be of interest.

A SPECIAL PROCEDURE TO DETERMINE Vm

The determination of Vm following the procedure described demands great accuracy in the determination of each of the functions shown in Fig. 9 as Vm is determined by the difference of these functions, ΔPec = f (ΔVtm) and ΔPtm = f (ΔVtm) respectively This difference can be studied more directly by following another procedure providing greater accuracy in the Vm determination.

The chamber pressure is raised to e.g 5 cm H_2O and the subject equilibrates, resulting in the situation shown in Fig. 12 a. The ear is then connected to the atmosphere producing a $\Delta Pec_3 = -5$. This will pull the tympanic membrane outwards resulting in ΔVtm_5 that cannot be recorded. The subject then equilibrates (Fig. 12 b to c) producing ΔVtm_6, ΔPtm_6 and ΔPm_6 when a gas portion enters the middle ear The Pch is then brought back to atmospheric. At last the subject equilibrates producing a $\Delta Pm_7 = -5$ cm H_2O and a ΔVtm_7 that is recorded.

ANALYSIS OF THE PROCEDURE

At the equilibration leading from Fig. 12 d to e the $\Delta Pm_7 = \Delta Ptm_7 = -5$ cm H_2O and the corresponding ΔVtm_7 are recorded (in the example illustrated $\Delta Vtm_7 = 8$ 6 microliters) This gives one point in the pressure-volume diagram of the tympanic membrane.

The position of the membrane in Fig. 12 c is thus known to be ΔVtm_7 from its neutral position.

The event leading to *c* was an equilibration (*b* to *c*) at which the ΔVtm_6 was determined (in the example illustrated $\Delta Vtm_6 = 1$ 7 microliters) Knowing the membrane position at *c* (8 6 microliters) this position at *b* must then be 8 6 − 1 7 = 6.9 microliters. But the event leading to this situation was $\Delta Pec_3 = -5$ cm H_2O thus causing a volume displacement of the tympanic membrane of 6.9 microliters These data yield one point in the diagram describing the pressure volume behaviour of the complete middle ear ΔPec = f (ΔVtm) The procedure is then repeated at varying Pch and the data are shown in Fig. 13 a and b which is analogous to Fig. 9 a and b

The middle ear volume, Vm, is then calculated as shown above. Theoretically the data in Fig. 9 and Fig 13 are the same. But the data in diagrams *a* and *b* in Fig 9 are determined independently of each other and the error in one of them does not interfere with the other which is an advantage in many cases. In Fig. 13 is the diagram *a* determined directly and *b* is determined starting out from diagram *a* thus containing the same error As Vm is actually calculated starting out from a difference between Pec and Ptm respectively at a certain ΔVtm, the latter procedure is of advantage in determination of Vm.

If Vm is calculated by the procedure discussed, starting out from different ΔVtm in Fig. 13 the result will be almost the same (Vm mean 6350 range 6050–6550 microliters) which shows the accuracy of the method.

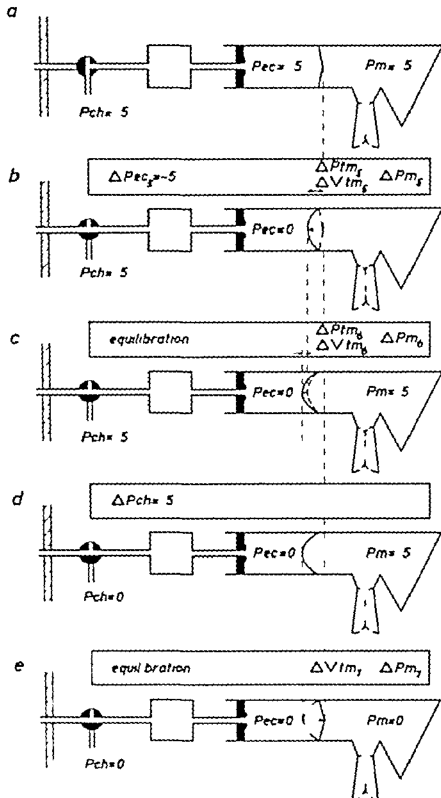


Fig. 1. The special procedure for determination of the volume of the ear space.

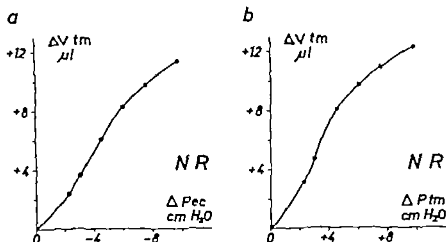


Fig. 13 Data analogous to Fig. 9 from the special procedure for determination of Vm.

THE ACCURACY OF THE VOLUME DETERMINATION— A COMPARISON BETWEEN THE DIRECT AND INDIRECT METHODS

THE INDIRECT METHOD

The accuracy of the volume determinations performed with the indirect method described above appears from table II. Six determinations at different ΔVtm values were made.

Table II.

Subject	Vm mean, in microliters	Vm range, in microliters
A.M.	3300	3120–3370
N.R.	6350	6050–6550
I.A.	7200	7000–7900
F.A.	6500	6200–6700
I.T	5100	5010–5200

THE DIRECT METHOD I.E. AFTER AN INCISION OF THE TYMPANIC MEMBRANE

The closed middle ear cavity is then expanded by a known volume change resulting in a lowering of the pressure in the closed system, which is recorded. The ear volume is calculated according to Boyle's law (Flisberg, Ingelstedt and Örtegren 1963). But there are some sources of error which must be analyzed when using the direct method. The airtight connection in the bony external ear canal must be absolutely fixed. This is illustrated as follows. In the first direct volume determination on A.M. a rubber disc of a diameter of 4 mm was introduced into the ear canal. Then the volume of the closed ear

space up to the disc was determined at 6000 microliters. This volume was very high in relation to the value indirectly determined (3300 microliters) Therefore a new disc with a diameter of 5 mm was introduced. Now the volume was determined at 3600 microliters which seems to be accurate since a small air space outside the membrane is included. The error involved by using the smaller rubber disc can be explained as follows When the underpressure of about −4 cm H_2O during the volume determination is applied to the closed ear-manometer system the smaller rubber disc slides or bulges inwards which results in a volume displacement of about 10 microliters i e a distance of 0.2 mm. This small" movement gives an erroneous increase of the ear space volume determination of 2400 microliters!

In model experiments such errors of the volume determination are reproducible when using a too small rubber disc. The error may not be appearent from a large range of the repeated determinations as the volume displacements of the disc may be quite reproducible. This error produced by a movable rubber disc is however avoided when the indirect method of determination is used as the pressure across the disc does not change at the moment of fVtm-determinations

SUMMARY

When the extratympanic pressure changes this will cause a movement of the tympanic membrane Now as long as the ear space behind the membrane remains closed, i.e the Eustachian tube does not open, each movement of the tympanic membrane will change the volume of the enclosed gas This volume change will in its turn change the pressure in the closed ear space. Serial recordings of the volume displacement of the tympanic membrane caused by varied changes in the extratympanic i.e. the ambient pressure have been performed.

The pressure volume relationship of the tympanic membrane under static and dynamic conditions is determined. No hysteresis of the pressure-volume relationship could be observed.

With the aid of different values determined from both these types of recordings two pressure-volume diagrams are constructed from which the volume of the air-filled ear space the middle ear pressure and the volume of the air portion passing through the Eustachian tube can be quantitatively calculated on intact ear drum cases.

A comparison between the direct and indirect methods for the volume determination of the air-filled ear space shows that the volume is more accurately determined indirectly This is due to the fact that the occluding cuff in the external ear canal easily moves when the direct closed manometry is applied to the canal after a drum incision. The movement of the cuff is probably due to the fact that a pressure change must be produced across the cuff during this type of volume measuring procedure

4 Quantitative determination of the tubal ventilation during changes in ambient pressure as during ascent and descent in aviation

Ingelstedt and Jonson (1966) showed that the volume of gas entering the middle ear at a moment of tubal opening (ΔVt) can be expressed as

$$\Delta Vt = \frac{Vm \cdot \Delta Pm_i}{Pm_t} + \Delta Vtm \qquad \text{eq 11}$$

At changing ambient pressure the determination of ΔVtm caused by tubal opening involves difficulties because of 1) compression of the gas in the external ear canal and in the connection to the flowmeter 2) continuous volume displacement of the tympanic membrane

During increasing ambient pressure (Fig. 14 a) there is therefore a continuous flow component through the flowmeter towards the ear

At moments of tubal opening (Fig. 14 b) the tympanic membrane springs back towards its neutral position, i e. outwards. This causes a flow component in the direction out from the ear causing a transient reversal of flow through the ear canal and the flowmeter This ΔVtm caused by a ΔVt is thus in the recording superimposed on the slow continuous flow component discussed above. The recording of the volume displacement is therefore extrapolated from the moment of beginning pressure equilibration (interrupted line) The ΔVtm resulting from a ΔVt is read as the maximum difference between the recorded volume signal and the extrapolated line describing what would happen if no tubal opening had occurred. The extrapolation may be slightly erroneous because of the alinear shape of the volume tracing (compare alinear $\Delta Vtm/\Delta Ptm$ relationship) but such errors are disregarded as the extrapolation covers a short time. Since the ΔVtm at such a moment is known the ΔPtm may be derived from Fig. 9 b.

From equation 5 follows that $\Delta Ptm = \Delta Pm$ (chamber pressure is regarded as constant at the equilibration moment) Knowing Vm, ΔPm and ΔVtm ΔVt may be calculated using equation 11

In chapter 3 a way was demonstrated to predict the changes occurring in the middle ear system at changing ambient pressure as long as the Eustachian tube remains closed. Such predictions are based on determination of the mechanics of the middle ear in each actual subject In this paper we have shown that changes of the middle ear variables may be determined at moments of tubal opening

Combining predictions of the course of events during periods of a closed Eustachian tube and determinations of events at moments of an open tube we

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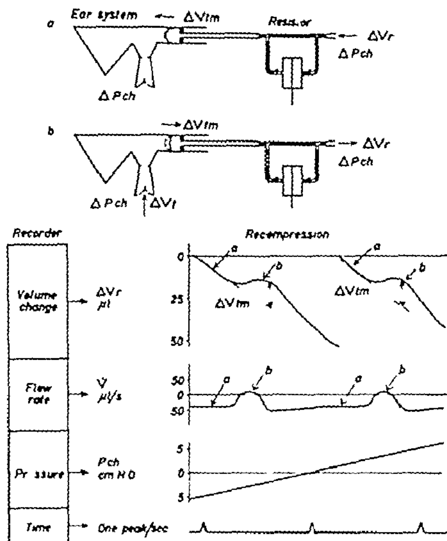


Fig. 14 Principles for determination of ΔVtm at changing ambient pressure

may proceed to a study of the course of events during changing ambient pressure with intermittently open Eustachian tube

Such a study is illustrated in Fig. 15 The pressure in the chamber Pch is lowered to −50 cm H_2O and the subject is allowed sufficient time completely to equilibrate the pressure in the middle ear i e the tympanic membrane is in its neutral position, Pm = Pec When, at moment *a* the pressure in the chamber begins to rise again (recompression) the course of events until the first moment of tubal opening (moment *b*) may be predicted starting from Fig. 9 a This prediction is shown in Fig 15 a to b in interrupted lines in the ΔVtm-diagram.

At the moment of tubal opening (Fig. 15 b) the ΔVtm is recorded and the ΔPtm = ΔPm is obtained from Fig. 9 b The ΔVt is calculated according to equation 11

The changes at the moment of tubal opening are in the ΔVtm-diagram of

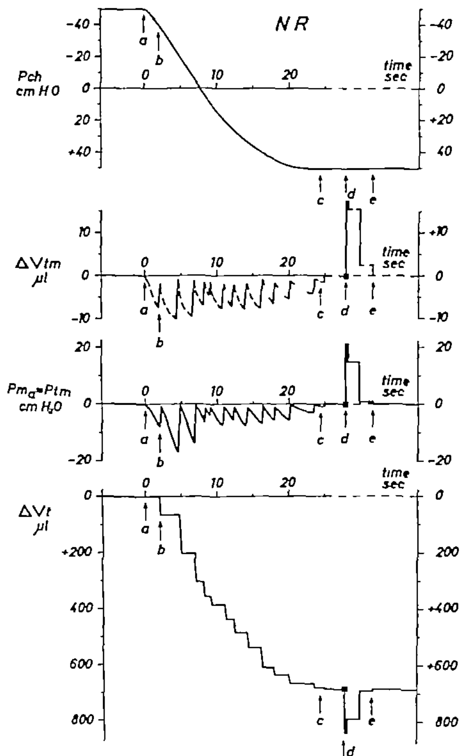


Fig. 15. Events in the middle ear at increasing ambient pressure descent, as determined on subject N.R.

Fig. 15 shown in continuous line at *b* where the predicted (interrupted) line ended at the moment of tubal opening. Thereafter the prediction starts again until the next tubal opening and so on. At moment *c* the pressure in the chamber has reached its final +50 cm H_2O From Fig. 15 it is obvious that at this moment the subject has equilibrated his middle ear pressure to ambient pressure. The subject has been able to keep his middle ear pressure close to ambient pressure during the flight" The summed total ΔVt during the flight will amount to 685 microliters which is very close to the calculated volume required to change the middle ear pressure to the new ambient pressure according to Boyle s law (eq 7) When it is assumed that the middle ear pressure is equilibrated to the new ambient pressure of +50 cm H_2O the subject is instructed to perform a Valsalva manoeuvre against his clamped nose. A highly positive ΔVtm is recorded resulting from an air portion being forced into the middle ear Then the subject equilibrates stepwise during deglutition. In the present case the tympanic membrane returns at moment *e* to the same position as that at moment *d* This is interpreted as further evidence that the subject really had equilibrated his Pm completely already at moment *d*

The described method for continuous determination of middle ear events is further discussed in the general discussion (chapter 7)

SUMMARY

If the mechanical properties of the middle ear system are known, recordings of volume displacements of the tympanic membrane during flights provide information that allows determinations of the continuously changing middle ear pressure and the tubal ventilation during changing ambient pressure simulating ascents and descents in diving and aviation.

5 Studies on the ventilatory function of the Eustachian tube during changes in ambient pressure in pilots

SUBJECTS

N.R. 24 years old, jetplane pilot. Never any aural symptoms. Normal findings in ears, nose and throat. Normal audiogram. The tube opens at a pressure below +5 cm H_2O delivered to the nose during the act of swallowing The volume of the closed air-filled ear space (Vm) 6350 microliters. During descents he usually makes his tubes patulous at will. But he can also open the tubes intermittently by making frequent elevations of the soft palate and the base of the tongue during the descent.

J.A., 23 years old, jetplane pilot. Never any aural symptoms. Normal ear nose and throat findings. Normal audiogram. The tube opens at a pressure below +5 cm H_2O delivered to the nose during the act of swallowing. The closed volume of the air-filled ear space (Vm) 7200 microliters During descents he regularily opens his tube by making frequent elevations of the soft palate and of the base of the tongue.

F.A., 27 years old. Flying officer experienced jetplane pilot. Regular troubles of the left ear during descents. Can always eliminate the troubles but only by making repeated Valsalva manoeuvres when clamping his nose Normal ear nose and throat findings. Normal audiogram. The tube opens when tested at a pressure below +5 cm H_2O delivered to the nose during the act of swallowing The volume of the left air-filled ear space (Vm) 6500 microliters.

J T 22 years old, flying cadet. 2 years of training on piston-engined plane. Short history of left-sided acute otitis media as a child. Regular troubles with left ear during descents. These troubles can easily be eliminated but only by making Valsalva manoeuvres while clamping his nostrils. However he "has not always time to perform the manoeuvres Never any trouble with his right ear Normal findings in nose, throat and right ear The left tympanic membrane is flaccid. Normal audiogram. Both tubes open at testing with a pressure below +5 cm H_2O delivered to the nose during the act of swallowing The volume of the left closed air-filled ear space (Vm) 5100 microliters. The left ear of J T was studied in this report.

The four subjects were examined with respect to the static middle ear mechanics according to the principles discussed earlier The result is presented in Fig. 16 a and b Fig 16 b shows the pressure volume relationship of the tympanic membranes. Three of the subjects (N.R. J.A. and F.A.) have normal

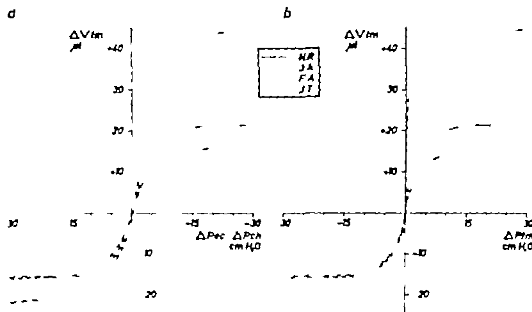


Fig. 16. Data analogous to those in Fig. 9 determined on the four pilots.

elastic properties of the studied tympanic membrane. Subject J.T., however shows a very large membrane volume displacement from its neutral position at a slight pressure across the tympanic membrane, i.e. the membrane is very flaccid which was also confirmed by inspection. The subjects were then tested during flights i.e. changes in ambient pressure simulating ascents and descents. The events taking place in the middle ear were studied according to principles discussed in the previous paper. The subjects were instructed to make pharyngeal manœuvres during the "flight" in order to equilibrate the middle ear pressure.

RESULTS

The different simulated flights were repeated 3 or 4 times and the findings were reproducible. Fig. 17 and Fig. 18 illustrate the course of events during increasing ambient pressure, descent, in the two pilots without any ear troubles. They succeeded in keeping the tympanic membrane close to its neutral position and the pressures in the middle ear close to the changing ambient pressure by frequently admitting adequate air portions to pass through the Eustachian tube. The volume of air passing through the Eustachian tube required for keeping the middle ear pressure exactly at ambient pressure is shown in the lowest diagrams in Fig. 17 and Fig. 18 in interrupted lines. At the final ambient pressure (+45 resp. +50 cm H_2O) N.R. has completely equilibrated his Pm. J.A. has a very slight residual negative Pm, and the tympanic membrane correspondingly deviating from the neutral position. This is further shown by the

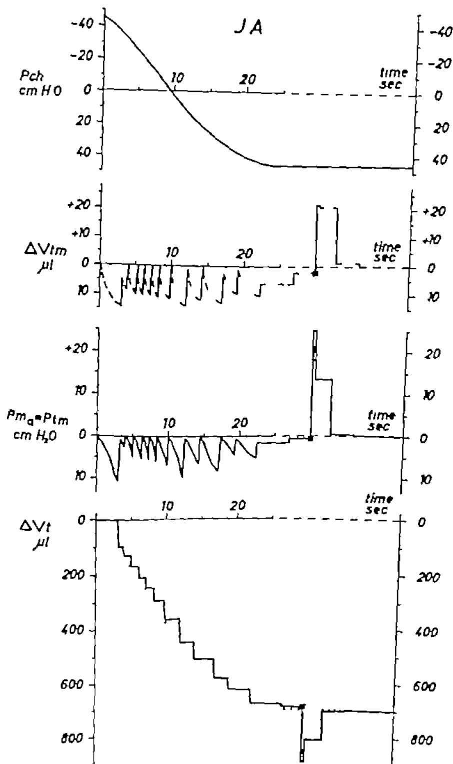


Fig. 17. Events in the middle ear at increasing ambient pressure. Subject J.A.

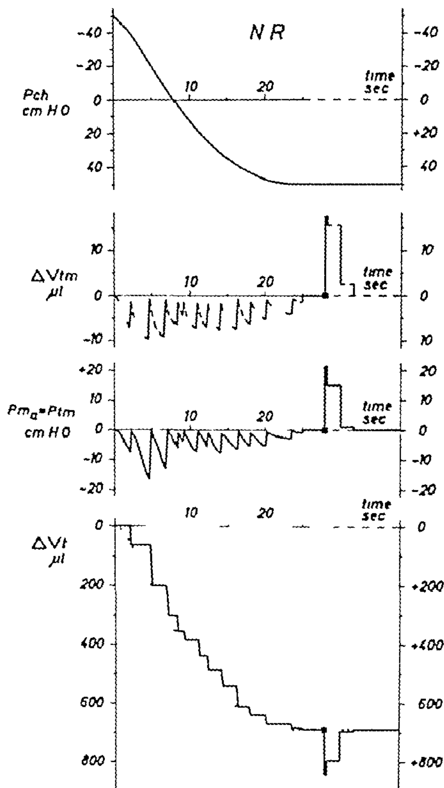


Fig 18 Events in the middle ear at increasing ambient pressure Subject N.R.

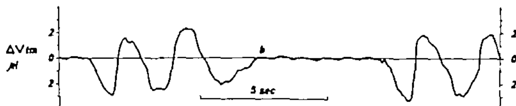


Fig. 19 Tracing illustrating the movements of the tympanic membrane synchronous with respiration when N.R. makes his tube patulous at will (a–b)

fact that this position of the tympanic membrane is not regained at the equilibration following the Valsalva manoeuvre when it is taken for granted that the tympanic membrane does return to its neutral position.

It should be observed that during actual flights pilot N.R. uses another method to keep his Pm at ambient pressure, namely by making his Eustachian tube patulous. This ability is verified in a recording of ΔVtm at constant ambient pressure (Fig. 19) The tympanic membrane performs movements synchronous with the respiration, which movements are caused by pressure variations in the rhinopharynx when the Eustachian tube is made patulous at will (*a* to *b* in Fig. 19) When the Eustachian tube is again closed (*b* to *a*) only small pulse synchronous movements of the tympanic membrane are recorded.

Subject F.A. shows another pattern during increasing ambient pressure, descent (Fig. 20) Only few equilibrations occurred, the first one only after Pm_t had reached -50 cm H_2O The following equilibrations occurred at successively decreasing Pm_t. At every tubal opening, however an air portion, ΔVt, large enough to admit nearly complete equilibration, entered the middle ear At the final pressure altitude complete equilibration was rapidly achieved.

Studies in the fourth subject, J T with the most severe ear troubles resulted in the pattern shown in Fig. 21 during descent At the very beginning of the pressure increase the tube was frequently opened, but too small air portions were admitted to equilibrate the middle ear pressure completely and to keep the tympanic membrane at its neutral position. Later the frequency of tubal openings was successively lower and the relative underpressure in the middle ear was further built up At the final pressure Pch, the subject succeeded in equilibration of Pm_t only after several tubal openings.

Studies were also performed at decreasing ambient pressure, i.e. ascents Subjects N.R. and J.A. showed a similar pattern as during descents, i.e. by frequently and efficiently opening the tube the tympanic membrane was kept close to its neutral position and the Pm was kept close to the ambient pressure (Fig. 22) Subjects J T and F.A., however showed only small and less frequent equilibrations (Fig 23) After reaching the final chamber pressure the tympanic membrane returned to its neutral position only after several tubal openings. Calculations of the gas volumes that had left the middle ear at the

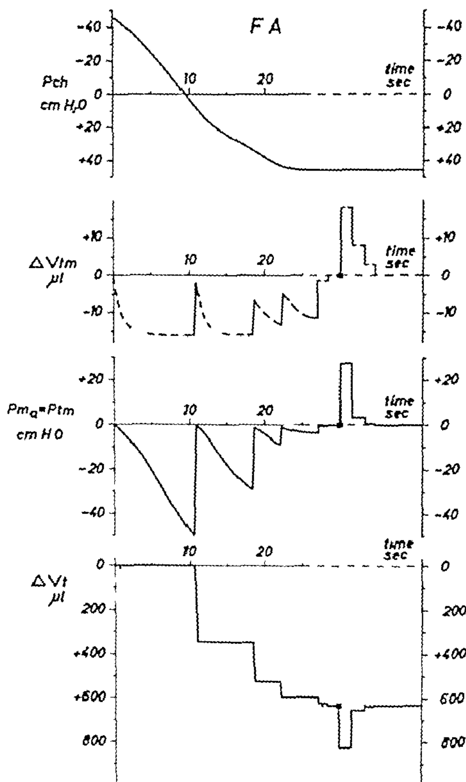


Fig. 20. Events in the middle ear at increasing ambient pressure. Subject F.A.

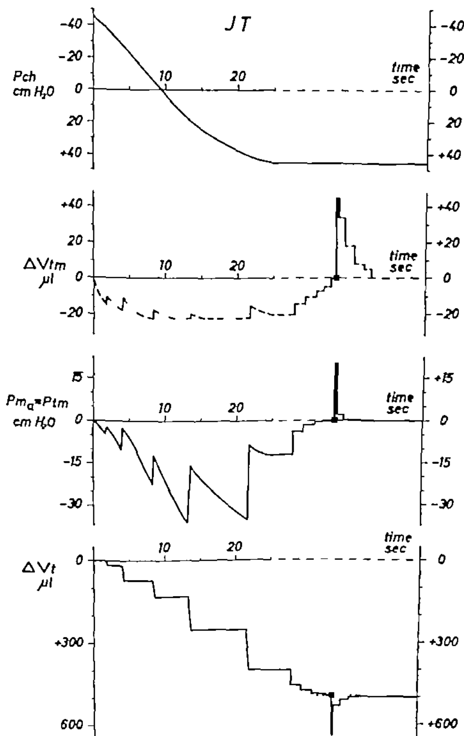


Fig. 21 Events in the middle ear at increasing ambient pressure. Subject JT

6 The effect of changing body position on the function of the Eustachian tube

Determination of the course of events at increasing and decreasing ambient pressure was made in the dorsal recumbent position in subjects N.R. and J.A., both with a good Eustachian tube function, and in subject F.A., with a less good Eustachian tube function.

In Fig. 24 the events at decreasing ambient pressure are compared with the corresponding result in sitting position. The frequency of successful equilibrations decreased in subjects N.R. and J.A. Subject F.A. did not actively open his tube at all in the recumbent position. Fig. 25, 26 and 27 shows the same comparison at increasing ambient pressure. The variations of Pm = Ptm are also shown. The same tendency towards fewer successful openings of the Eustachian tube was observed. N.R. and J.A. equilibrated their Pm almost completely at most equilibrations, as they did in the sitting position. As a consequence of less frequent equilibrations, however, the mean Pm, during the descents, as shown in Fig. 25–27, deviated more from ambient pressure in the recumbent position than in the sitting one. Subject F.A. performed only two tubal openings during the descent and on those occasions the Pm was not completely equilibrated, as was the case in the sitting position.

The experiments in the different positions were repeated several times and the tendencies observed were consistent.

DISCUSSION

Lucae (1866) is supposed to be the first to observe that the patency of the Eustachian tube was dependent on the position of the head. He found that the positive pressure in the rhinopharynx needed to force the tube open was higher when the head was bent backwards than when it was bent forwards. Hartmann (1878) and Perlman (1943) showed that this pressure was increased in different circumstances such as pressing the head down on the chest, twisting the head to one side, pressure on the neck, compression of the jugular vein and assumption of a prone position. It is also known that a patulous tube is commonly closed when the subject is lying down. Also the present study showed that the function of the Eustachian tube was hampered by the recumbent position, even in normal pilots who have to equilibrate the middle ear pressure by profession. It also shows that the present method allows determination of small changes in tubal function.

It is likely that an increase of the capillary venous pressure, causing engorge-

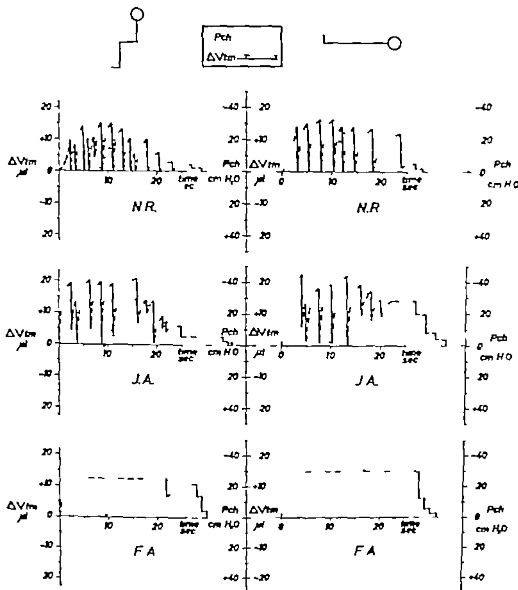


Fig. 24 Effect of the body position on the tubal ventil tion at decreasing ambient pressure. Subjects N.R., J.A. and F.A.

ment of the vessels in the mucosa and mucosa swelling, is at least in part responsible for the referred phenomena

Studies of the ventilatory function of the Eustachian tube in the recumbent position are of special interest. Slight dysfunction of the Eustachian tube may be more easily revealed if tests are performed during unfavourable conditions e.g. in the recumbent position

It also seems important that the tube does function during such conditions In aviation the crew is often subjected to gravitational and great accelerative

Fig 25 Effect of the body position on the tubal ventilation reflected by the variations of Pm at increasing ambient pressure Subject N.R.

Fig 26 Effect of body position on the tubal ventilation reflected by the variations of Pm at increasing ambient pressure. Subject J.A.

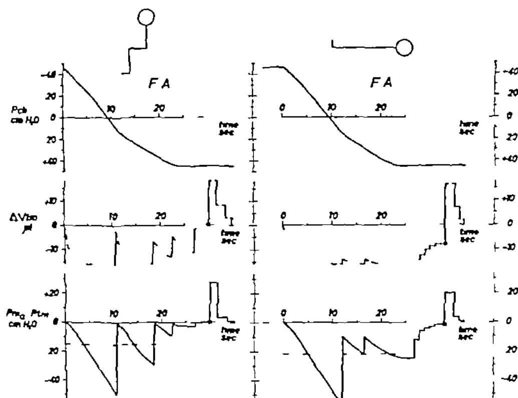


Fig 27 Effect of body position on the tubal ventilation reflected by the variations of Pm at increasing ambient pressure. Subject F.A.

forces in different directions relative to the body position, and the phenomenon discussed may be of importance. Diseases may be regarded as secondary to tubal dysfunction thus acute otitis commonly starts at night during sleep Possibly the reason may be that the increased venous hydrostatic pressure causes an increased engorgement of the mucosa resulting in tubal dysfunction, which dysfunction might be revealed along the lines discussed.

SUMMARY

Comparative tests of the Eustachian tube function were performed in the sitting and in the dorsal recumbent position. This function was hampered by the recumbent position even in pilots with a normal Eustachian tube function. This phenomenon is supposed to be due to an increased capillary venous engorgement in the tubal mucosa and considered to be of pathophysiological importance

7 General discussion

Several physiological mechanisms contribute to the shaping of the pressure variations in the middle ear The most important of these are resorption of gas from the middle ear the function of the Eustachian tube, the mechanical properties of the ear drum system, the volume of the gas filled ear space and the volume changes of the mucosa of the middle ear

Studies on the regulation of the middle ear pressure have earlier been hampered by methodological difficulties to determine this pressure and the different mentioned variables related to it. The need for puncture of the middle ear characteristic of the direct method for the pressure determination, limits the use of such methods The indirect methods hitherto used for example the pneumophone method, demand that the pressure in the external ear canal is equilibrated with the pressure in the middle ear This limits the use of such methods as the pressure in the middle ear can be measured only in static conditions The validity of this methods is also limited, which is shown in chapter 3 Aware of these limitations the present authors consider some of these methods to be of great value in many applications as they may be very easy to use

Regarding the limitations of earlier methods the present authors have developed indirect methods to determine properties of the middle ear and events taking place within it even under dynamic conditions such as aviation or diving in a pressure chamber One of the purposes of such studies was to evaluate if tests performed during surrounding pressure variations would reveal slight functional disturbances that would not be revealed in static conditions The presented methodological approach is based on registration of movements of the tympanic membrane revealed by volume displacement in the external ear canal which are sensed by a flowmeter integrator system. All determinations of properties or events of the middle ear are calculated starting out from the registered volume displacements of the tympanic membrane For example the position of the tympanic membrane is at any moment supposed to reflect the pressure in the middle ear in accordance with the pressure volume diagram of the drum, determined in every case The calculations of different variables are based upon equations which include some assumptions and approximations The pressure-volume behaviour of the tympanic membrane is supposed to be without hysteresis. Evidence for this is shown. No changes of the mucosa volume caused by middle ear pressure variations of short duration are supposed to occur It is shown that this is a reasonable approximation in normal ears Such an approximation may however be grossly erroneous in cases with

for example hyperaemia of the middle ear mucosa or in cases with small cell systems.

The use of a flowmeter connected to the external ear canal is of great advantage compared to the manometer system earlier used in the method called closed manometry presented by Flisberg, Ingelstedt and Örtegren (1963). In this method the volume displacement of the tympanic membrane was revealed by pressure variations in a closed volume connected to the external ear canal. Such pressure variations however slightly affect the tympanic membrane and may even affect the occluding cuff (see chapter 3). Difficulties may exist in calibration as the relation between adiabatic and isothermal compression of the enclosed gas may differ at different frequences. The system is further extremely sensitive to temperature changes. These difficulties would be overcome if the method was further developed, but the method cannot be used in conditions simulating aviation as the tympanic membrane is not subjected to the changing ambient pressure.

An investigation on a subject is made in two stages by the present method. The first is to examine the static properties of the middle ear, i.e. the pressure-volume relationship or the elastic properties of the tympanic drum and the volume of the gas in the middle ear. Knowledge of these factors are in themselves of great physiological and patophysiological interest and is a prerequisite for the subsequent stage in which physiological events are studied. These studies allow continuous determination of the ear drum position, of the pressure in the middle ear and of the tubal ventilation during changes in surrounding pressure simulating aviation or diving. The influence of body position on the tubal function is easily shown, indicating that test of different factors affecting tubal function may be studied in detail with the present method.

Studies of the tubal ventilation at constant surrounding pressure, reflecting resorption of gases from the middle ear would also be possible according to the principles described by Ingelstedt and Jonson (1967) but made with the present nontraumatic technique.

The method described has some inherent limitations of importance besides the approximations used in the different calculations. The first stage discussed above demands a reasonably well functioning Eustachian tube allowing the subject completely to equilibrate his middle ear pressure at least after repeated swallowings. Cases without this ability must be examined according to other principles.

With the present method for determination of volume displacements of the tympanic membrane at changing surrounding pressure the volume changes of the gas in the external ear canal and the catheter system introduces difficulties at very rapid pressure changes. The present investigation shows recordings of the events at pressure changes of 3 meters of water per minute corresponding to 100 km/hour vertical ascent or descent in aviation. The accuracy in the determination of these events is shown by the figures of summed tubal ventilation during the pressure changes, which correspond well to the volume needed according to Boyle's law. The mentioned rate of pressure change should not

be regarded as the upper limit inherent in the method. The diffusion of gases between the middle ear and the blood is slow at ground conditions and air breathing (Ingelstedt and Jonson 1967) and has been neglected in the present experiments on "aviation During prolonged ascents or descents covering great changes in surrounding pressure or at changing composition of the inhaled gas, the diffusion gradients and thus the rate of diffusion may be grossly increased. In such cases the diffusion of gases may significantly contribute to the gas exchange of the middle ear and should not be neglected.

The equipment necessary for tests of the type presented is not very complicated. The big pressure chamber allowing the investigator to be in close contact with the subject, although invaluable in developing the present and other techniques, is not inevitable and, for routine tests may well be replaced by a pressure body box connected to a reversible fan

The zeroline drift of the flow recording must be extremely small to allow integration over long periods of time without disturbing drift of the volume signal. After precautions discussed in chapter 1 had been taken, the electronic equipment used (Elema Schonander Sweden) fulfilled high demands in this respect.

The importance of a well fitting cuff correctly placed in the bony part of the ear canal by the trained doctor should be stressed. After the methodological problems discussed above have been solved, the method is quite easy to use even in routine practice by ordinary lab assistants.

The gas volume of the middle ear the elastic properties of the tympanic membrane and the pressure volume behaviour of the middle ear mucosa are three properties of the middle ear which contribute to determine the effect of gas resorbtion from the middle ear of tubal equilibration of the middle ear pressure and of changing surrounding pressure These static properties and their physiological significance in two hypothetical cases may be illustrated by three pressure-volume diagrams, Fig. 28 a b and c. Fig 28 a shows the expansion of the middle ear gas, ΔVm at changing middle ear pressure ΔPm. This relationship is dependent on the middle ear gas volume according to equation 7 i.e Boyle s law

Fig. 28 b shows the volume displacement of the tympanic membrane ΔVtm, caused by the pressure across it, ΔPtm that equals ΔPm if surrounding pressure is constant.

Fig 28 c shows the volume changes of the middle ear mucosa, $\Delta Vmuc$, at changing middle ear pressure.

Figure 28 shows two hypothetical cases, X with a normal ear drum and a normal middle ear volume (7 ml) and Y with a flaccid ear drum and a small cell system (3 ml) When gas enters or leaves the middle ear via the Eustachian tube at tubal opening, ΔVt or via diffusion, $\Delta Vdiff$ during periods of closed Eustachian tube changes in Vm Vtm and Vmuc occur to make up for the gas volume entered or left, and a corresponding change of Pm = Ptm will result. The volume changes are represented by the equations (see equation 1)

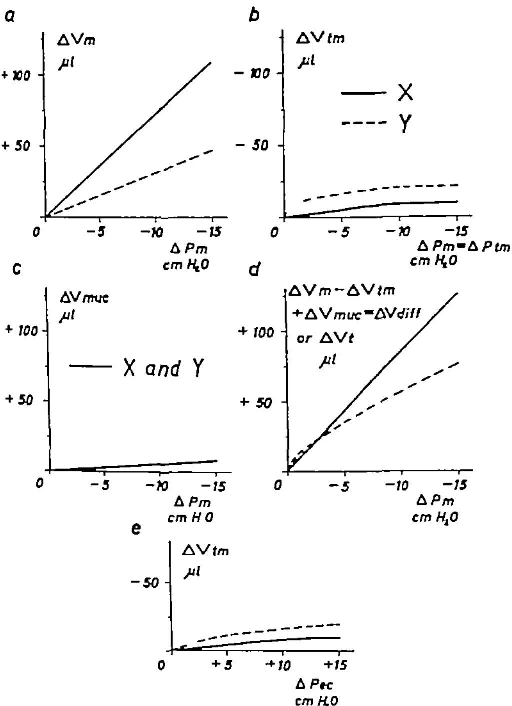


Fig. 28. Pressure-volume relationships of the middle ear in two hypothetical cases.

$$\Delta V diff = \Delta Vm - \Delta Vtm + \Delta Vmuc$$

or

$$\Delta Vt = \Delta Vm - \Delta Vtm + \Delta Vmuc$$

If the sum ($\Delta Vm - \Delta Vtm + \Delta Vmuc$) is calculated at different middle ear pressures a fourth pressure volume diagram can be constructed Fig 28 d. This diagram shows the relationship between gas volumes entering or leaving the middle ear and the resulting middle ear pressure Let us assume that 22.5 microliters of gas have been resorbed from the middle ear after the latest equilibration of the middle ear pressure in case X and Y In figure 28 d the resulting middle ear pressure is read to be −2.5 cm H_2O in both cases.

The data of ΔVtm and $\Delta Vmuc$ are read from diagram *a–c*

	ΔVdiff	ΔPm	ΔVm	ΔVm in % of ΔVdiff	ΔVtm	ΔVtm in % of ΔVdiff	ΔVmuc	ΔVmuc in % of ΔVdiff
subj X	22.5	−2.5	18	82	2.8	14	1.2	4
subj. Y	22.5	−2.5	7.5	33	13.3	63	1.2	4

In the *normal* case the *expansion of middle ear gas accounted for* 82 % of the volume changes caused by the gas diffusion as compared to 33 % in case Y in which case the ear drum accounted for most, i e 63 % of the volume change

The mucosa accounted for only a small fraction of the volume change in these examples

A fifth pressure volume diagram describing the volume displacements of the tympanic membrane ΔVtm, at changing pressure in the auditory canal ΔPec and a closed Eustachian tube is shown in fig. 28 e. This diagram can be constructed starting out from diagrams *a* and *b* Neglecting $\Delta Vmuc$ and $\Delta Vdiff$ at a rapid change in surrounding pressure $\Delta Vtm = \Delta Vm$. At a certain $\Delta Vtm = \Delta Vm$ ΔPtm and ΔPm can be read from diagrams *a* and *b* in Fig 28. But $\Delta Pec = \Delta Pm - \Delta Ptm$ (see equation 5) and the relationship between ΔPec and ΔVtm can thus be established, diagram *e* This diagram can be used in studies of events at changing surrounding pressure.

Suppose that the surrounding pressure suddenly increases by 10 cm H_2O Diagrams *e* and then *a* and *b* tell that

	ΔPec	ΔVtm	ΔPtm	ΔPtm in % of ΔPec	ΔPm	ΔPm in % of ΔPec
subj. X	10	− 8	8	80	2	20
subj Y	10	−16	5	50	5	50

This shows that in a normal ear the tympanic membrane will be loaded by most of the pressure change. If the ear drum is flaccid the pressure will increase more within the middle ear and the ear drum will be less loaded.

The above shows how the mechanical properties of the middle ear affect the events resulting from gas resorbtion from the ear tubal ventilation or surrounding pressure variations. It is obvious that the size of the middle ear cell system and the elastic properties of the tympanic membrane are of functional importance concerning the regulation of the middle ear pressure.

To which extent and how these factors may also affect the ventilation of the middle ear via the Eustachian tube is not known. It is also little known how different diseases of the middle ear affect the tympanic membrane and the volume of the cell system. With the methods presented such knowledge would be obtainable as measurement and functional analysis may be repeated any number of times.

General summary

1. Methods in studies of middle ear pressure and related variables were discussed.
2. The relationships between middle ear pressure middle ear gas volume tympanic membrane elasticity and mucosa volume changes were discussed.
3. A pressure chamber and a method based on air flow measurement for determination of tympanic membrane volume displacement were described.
4. The effect of changing middle ear pressure of the aural mucosa volume and its significance in middle ear studies were evaluated.
5. A non-traumatic method for determination of the elastic properties of the ear drum system and the volume of the air-filled middle ear space was described.
6. A way was shown how to calculate quantitatively the ventilation through the Eustachian tube from the registered movements of the intact tympanic membrane—the elastic properties of the drum and the volume of the middle ear air space being known.
7. In 4 pilots the tubal ventilation and the middle ear pressure were continuously determined during changing ambient pressure simulating aviation.
8. Different normal and abnormal modes of function of the Eustachian tube during ambient pressure changes could be demonstrated
9. The effect of body position on tubal ventilation could be analyzed
10. Methodological and biological aspects of the present investigations were discussed.

Zusammenfassung

1. Methoden für die Untersuchung des Druckes und der Eigenschaften des Mittelohres werden diskutiert.
2. Die Beziehungen zwischen Druck und Gasvolumen im Mittelohr sowie Elastizität des Trommelfells und Volumenschwankungen der Schleimhaut werden diskutiert.
3. Es wird eine Druckkammer und eine Methode für die Bestimmung der Volumenverdrängung durch die Trommelfellbewegung mit dem Prinzip der Luftstrommessung beschrieben.
4. Der Effekt der Änderung des Mittelohrdruckes auf das Schleimhautvolumen und deren Bedeutung bei Mittelohruntersuchungen werden untersucht.
5. Es wird eine atraumatische Methode für die Bestimmung der elastischen Eigenschaften des Trommelfellsystems (Trommelfell und Gehörknöchelchenkette) und des Volumens des luftführenden Mittelohrraumes beschrieben.
6. Es wird eine Möglichkeit gezeigt, quantitativ die Ventilation durch die Eustachische Röhre zu kalkulieren durch die Registrierung der Bewegung des intakten Trommelfells unter Voraussetzung von Kenntnissen über die elastischen Eigenschaften des Trommelfellsystems und des Luftvolumens des Mittelohrraumes.
7. Bei 4 Piloten wurden die Tubenventilation und der Mittelohrdruck kontinuerlich bestimmt bei laufender Veränderung des Umgebungsdruckes im Sinne der Simulation eines Flugverlaufes.
8. Es konnten dabei unterschiedliche normale und anormale Formen der Ohrtrompetenfunktion bei Veränderung des Umgebungsdruckes demonstriert werden.
9. Der Einfluss der Körperstellung auf die Tubenventilation konnte analysiert werden.
10. Methodische und biologische Aspekte der vorliegenden Untersuchungen werden diskutiert.

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VESTIBULAR FUNCTION AND ADDITIONAL FINDINGS IN WAARDENBURG'S SYNDROME

RICHARD E. MARCUS

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ACTA OTO-LARYNGOLOGICA

SUPPLEMENTUM 229

VESTIBULAR FUNCTION AND ADDITIONAL FINDINGS IN WAARDENBURG'S SYNDROME

RICHARD E. MARCUS

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she had anomalies of the skull nose root, palate, teeth and jaws, as well as the skeletal deformities characteristic of Rocher Sheldon s syndrome

It was now apparent to Waardenburg that something more than coincidence was operative in the findings of deafmutism and the eyelid deformity in the 7 cases, particularly in view of van der Hoeve s uniovular twins and Walsh s brother and sister He enlisted the aid of the administrators of 5 Dutch institutes for the deaf and was able to examine 1050 individual residents of these institutions.

It is worth while quoting Waardenburg directly

I was anxious to discover whether I should find cases of dystopia of the medial canthi and pigmentary anomalies among these deafmutes. As it developed the search led not only to a confirmation of this association but indicated the existence of a hitherto unknown human syndrome which may be described as a combination of 6 chief characteristics

1 Lateral displacement of the medial canthi (dystopia canthi medialis lateroversa) combined with dystopia of the lacrimal puncta and blepharophimosis.

2. Prominent broad root of the nose (hyperplasia radicis nasi)

3 Growing together of the eyebrows, with hypertrichosis of their medial portions (hyperplasia supercilii medialis)

4 White forelock as a form of partial albinism (leucismus pilorum or poliosis)

5 Heterochromia iridum totalis sive partialis, and

6 Deafmutism or a somewhat incomplete degree of congenital deafness (surditas congenita)

This syndrome was found in its entirety or in part throughout 14 pedigrees, one of which included his original patient, the deaf tailor who had never been a resident at any of the institutions studied Of the 13 pedigrees resulting from the study of residents of the institutions, one is only partially documented. Interestingly two of the twelve fully documented pedigrees present, in one instance the family of Goedbloed s patient and in the other the kinship and descendants of van der Hoeve s uniovular twins, who were by the time of Waardenburg's study 40 years old.

On the basis of his extensive and detailed investigations, Waardenburg concluded that this syndrome showed dominant autosomal inheritance was present completely in 12 cases of the 840 congenitally deaf people but the several component anomalies were present in varying combinations in many individuals in the families studied. The separate anomalies showed variable penetrance, and in 161 affected relatives 159 (99%) showed dystopia canthi medialis lateroversa, 126 (78%) prominentia radicis nasi, 73 (45%) hyperplasia supercilii medialis, 41 (25%) heterochromia iridum, 32 (20%) surditas congenita (congenital deafmutism) and 27 (17%) showed albinismus circumscripta pilorum In a statistical analysis of these figures, although agreeing that the various features described by Waardenburg seemed "to constitute a well demarcated genetic complex Cotterman felt there were indications of a "statistical independence between the several manifestations in the individuals possessing the genetic factor"

Waardenburg estimated that the syndrome accounted for about 1 43 per cent of all deafmutes in the Netherlands (a population incidence of 1 per 212,000 with deafness) but the irregularly expressed dominant form, with or without deafness, was present in 1 out of 42,000 people

Further he indicated that the syndrome could occur sporadically as the result of mutations, and he estimated the possible mutation rate as 1 per 270 000 gametes.

Finally Waardenburg showed the close association of the features of the syndrome in man to similar occurrences in other mammals, and he developed a position as to the theoretical possibilities of genetic and embryologic alterations responsible for the syndrome He did not however feel that there were any answers at the moment and hoped that other workers "will seek to confirm my findings" and perhaps provide additional information to help understand this interesting, important and puzzling syndrome

REVIEW OF THE LITERATURE

Since the documentation of the clinical features of this genetic syndrome by Waardenburg (and now bearing his name) there have been numerous case reports and a few comprehensive investigations of the syndrome

Most of the case reports and the studies have confirmed Waardenburg's findings and, since Keizer's communication, also from Holland, have come from many countries all over the world (Appendix A, Table 2)

In some instances (Galvez Montes Settelmayer & Hogan Jain & Chander) the case reports show all the features except deafness. On the other hand, in his study of residents of the school for the deaf in Prague Klenka found many of the features but not in any of the children did he find all of the syndromal characteristics. However Waardenburg has shown that there is variable penetrance and very few of the patients show all the features, a finding corroborated by many of the authors

In two other reports, the syndrome is shown to occur in connection with other syndromes (Stoller) and with albinism (Campbell) This latter feature is reminiscent of Klein's patient (1947 1950) seen by Waardenburg As a matter of fact there is a group of writers who feel that the partial albinism, or depigmented skin, should also be included Waardenburg himself considered this possibility (1951) but did not have an opportunity to view his patients unclothed (perhaps a limitation imposed on him by reason of his longstanding ophthalmological training and practice) As a result, a number of authors, particularly the French language group (France Belgium Switzerland) have spoken of this condition as "albinism partiel" and have attached Klein's name in some instances to make it the Waardenburg Klein syndrome Bischler refers to it as the Klein Waardenburg syndrome.

Fisch (1959) went a step further and in his study confirming and extending Waardenburg's findings, he additionally found a family which included early graying of the hair without the eyelid deformity but demonstrating a type of deafness with moderately severe loss for all frequencies, with a little better hearing for the lower octaves These findings, including the difference in the type of audiogram, prompted Fisch to announce the possibility of a new syndrome which his group provisionally call the "early greying syndrome

Some of the authors have indicated the possibility of specific facial features, Fisch describing a very prominent jaw seen also by Thorkilgaard, and extended by DiGeorge (1960) to include a typical Waardenburg's facies the dystopia large jaw upturned nose with prominent columella and a "cupid's bow mouth"

Partington (1964) has re-emphasized that the single most important feature of the syndrome is the dystopia canthorum and along with DiGeorge (1960) has given careful consideration to measurement of the inter inner canthal inter pupillary and outer canthal distances in normal persons of various age groups and different sexes. Unfortunately DiGeorge (1960) has given the distances in only one Negro, and the other reports in Negroes (Scott & Beukering de la Harpe Soussi Calinikos) and other races (Zelig Jain & Chander) have not specified these distances.

As is usually the case in a clinical condition, the typical instance is easy to define and in its original description would lend itself to rather precise diagnosis. However the problem of questionable or border line findings does tend to obscure some of the details, and since the syndrome may appear in association with other defects, there may be a blurring of boundaries. It is evident that under such circumstances, it becomes difficult to make the proper assessment and arrive at a satisfactory diagnosis.

Owsley in a survey of schools for the deaf in the United States has stated that the intelligence apparently is not affected (also Fisch 1959 DiGeorge 1960 Partington 1964) although studies in progress (Walczak) may indicate other possibilities.

It is not the purpose of this presentation, however to be concerned with the delineation of the syndrome since that is adequately covered by Waardenburg himself in his original paper again in 1957 and confirmed by the many reports. The differential diagnosis is covered well by Fisch (1959) DiGeorge (1960) Partington (1964) and Houghton (1964) Francois recent exhaustive study corroborates in all details Waardenburg's findings, and merely reduces the percentages of penetrability of the various features, but not their order of importance Robinson (1965) also has shown the intra familial variability of penetrance as a possible aid to genetic counselling The works of DiGeorge (1960) and Soussi have shown that isochromic blue irides are part of the syndrome since they occur in Negroes. Waardenburg himself suspected the isochromic blue eyes of his Caucasians might be part of the syndrome (1951 1957) and Thorkilgaard makes a convincing case

with his feeling that it is the hypoplastic iris stroma that is pertinent whether it is unilateral or bilateral.

Neither is it the purpose of this paper to consider the genetic aspects in detail, but is properly left for others or for another communication. The etiologic considerations are quite involved and not only the locations on the chromosome are discussed (Soussi) but theories as to embryonic alterations are offered by Waardenburg (1951) himself as well as McKenzie Fisch (1959) and DiGeorge (1960). Chromosomal studies (Partington, 1964) were normal.

EARLY OBSERVATIONS IN THE SYNDROME

Our interest has been centered on the deafness as part of the Waardenburg syndrome particularly in regard to the auditory and vestibular systems. Fisch (1959) was especially concerned with the deafness. He felt, in his sample of probands (not including relatives) who came to him because of their deafness, that

the most frequent combination was *deafness eyelid deformity and deep blue eyes* [his italics]. All other combination were less frequent. In eight cases there was no eyelid deformity. The combination of *all* [again his italics] signs of the *syndrome in a single individual is comparatively rare.*

Therefore when our patient, Mrs. T., with outward appearances of the syndrome came to our clinic in 1961 we began a study of this problem. We were particularly interested in the fact that she had no vestibular response along with her heterochromia, mild dystopia, broad nose root, white hairs at the medial portion of her eyebrows, and profound deafness. As we had been interested in vestibular function in all types of deafness, we decided to pursue the matter further. In addition, since Mrs. T came to the clinic with her children, we proceeded to test all of them and found various types of syndromal findings, as well as cochlear losses and unusually altered vestibular responses (Figs. 1, 2 and 3). It has been reported that so-called uncomplicated congenital sensorineural hearing loss generally is accompanied by normal vestibular function (Marcus, 1951) although some hereditary congenital losses may have abnormal vestibular function (Arnvig, 1955, 1959, Davey). In many cases this can be shown to be acquired (Marcus *et al.*, 1963). Also certain types of injury at birth may change cochlear and vestibular function (Rosenblut *et al.*, Torok) but in other instances only cochlear involvement occurs.

Vestibular function has been described by some of the authors in Waardenburg's syndrome, but not in detail and as far as search of literature on the subject is concerned, no x-ray tomography has been reported although

general roentgenographic studies were included by Fisch (1959) Thorkilgaard and DiGeorge (1960)

We therefore began to study Mrs. T's family and through her uncle Mr G W., included his branch as well to try to determine the relationship of the deafness and altered vestibular function in Waardenburg's syndrome.

METHOD AND MATERIAL

The family pedigree (Figs. 4 and 5) was obtained by personal interview from Mr G W., II 9 who is now 54 years old, and his wife II 10 Each gave information on the other members of the family In most instances, agreement between the two was readily obtained as to the various characteristics of the different individuals, particularly since each of them knew all the others. There were some disagreements, however and when these occurred it was usually as to age or perhaps as to hair color On all other characteristics the agreement was considered conclusive and as far as could be determined, was genuine. This was corroborated in an independent canvass by another group studying the family elsewhere from another point of view Furthermore neither of our groups knew that the other was doing the canvass until after it was completed

In review of the 53 members, 22 were seen personally and examined by the author and various consultants. Of the 31 not seen or examined because of death, distance or other factors, complete agreement as to syndrome features was reached by the informants in 28

In the 3 instances, disagreement was only as to whether there was a hair component, either white forelock or prematurely gray hair The other recallable components as to eye color and bilateral severe deafness were agreed upon The lid, eyebrow and nose root components are considered unrecallable, as well as moderate or mild bilateral or unilateral deafness. Obviously these are difficult to remember let alone assess.

Of the 22 seen and examined, the following procedures were done

---

Fig 1 Probanda (III 2) Mrs T sh wi g heterochromi with blu sect t 7 o lock on left iris, and a few whit yebrow hairs nea midline (A) Except f two residual low frequencies on the left, her udiogram (B) hows complete bilateral sensorineural loss.

Fig. 2. Oldest daughter and first-born hild (IV 1) f probanda, howi g bil teral blu irides with deep brown scleral ri gs (A) Her audiogram (B) show complet sensori eural loss on the left, but some profoundly reduced hearing t most frequ ncies n the right.

Fig. 3. Third daughter nd fourth-born hild (IV-4) of probanda. Pronounced heterochromia and some dyst pla I teroversa, particularly on ight (A) Her udiogram (B) shows profound bil teral sensorineural loss with most frequencies represented. Bone conduction probably is tactil sensation





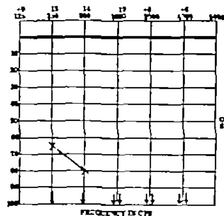
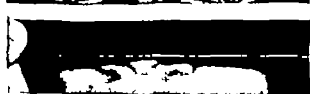


FIG. 1





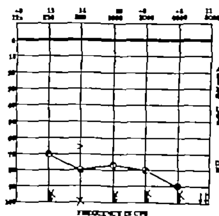


FIG. 2.



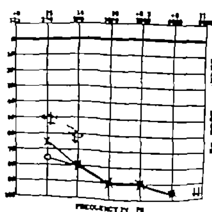


FIG. 3.

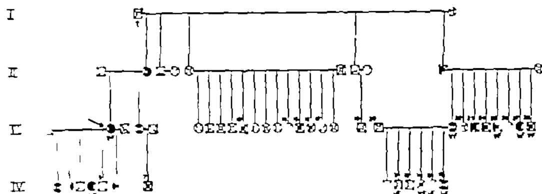


Fig 5 For e plan tion of ymbols see Fig 4

see if vestibular response would change in any way This was referred to as mass rotation Post rotatory nystagmus was observed under Bartel s glasses, noting frequency amplitude duration, and, where possible, total number of nystagmus beats.

Standards of vestibular function were set as follows

Normal More than 15 seconds of post rotatory nystagmus.

Moderately reduced. Between 5 and 15 seconds of post rotatory nystag mus.

Markedly reduced Less than 5 seconds of post rotatory nystagmus

Absent No observed response

Wherever possible depending on the age cooperation or availability of the patient, routine cold water caloric vestibular function tests were also used 10 cc of water at 68 F was instilled over a period of 5 seconds in each ear separately the contralateral ear after a five minute rest period The head was held in the 30 forward position with eyes closed for one minute including the instillation of water then brought back to the 60 extension position.

Where response to caloric test was in question it was repeated. Mass caloric tests were done wherever possible This was done by instilling 250 cc of 68 F water in each ear after 5 minute rest period

Observation of nystagmus was done through Bartel s glasses in proper light Stop watch recording was made of nystagmus including latency period, duration, frequency and amplitude Subjective sensation was also obtained by direct questioning

Standards of calorics were set as follows

Normal *Duration* 60–90 seconds (from time head placed at 60 flexion) *Frequency* 10 to 20 beats per 10 seconds (two separate 5 second periods at height of nystagmus about 20 seconds after onset)

Reduced *Duration* 40–60 seconds. *Frequency* 6–9 beats

Markedly Reduced *Duration* under 40 seconds. *Frequency* under 6 beats.

Absent No measurable response.

8. Hearing evaluation, both in the outpatient clinic and in the audiology unit using routine calibrated noise-makers in the sound field, pure tone audiometry where possible, or other special tests when indicated

Standards of auditory function were chosen as follows

Normal Within 15 db of International audiometric 0 in most frequencies or octave bands.

Moderately reduced 15 db–60 db, in most frequencies or octave bands.

Markedly reduced 60 db–100 db, in most frequencies or octave bands.

Absent No observed response

DESCRIPTION OF FINDINGS AND RESULTS

The survey of findings for the family are shown in Table 1 Of the total number of 53 in the four generations, 9 were congenitally deaf and these were all in the blood line since none of the family with issue, deaf or other wise married anyone who was deaf or who had signs of the syndrome.

Generation I

None was examined but I 1 reported as prematurely gray died at age 37 with normal hearing also his wife I 2 who had no other signs.

Generation II

II 2 (not examined) probanda s mother deceased, was congenitally deaf had either a white forelock or gray hairs at midline and had h terochromia Her two children, probanda and sister were both congenitally deaf

II-3 (not examined) deceased, was deaf and had premature graying of the hair He married but died without issue

II-5 (not examined) was normal, married, and is reported to have had thirteen children, one deceased, cause unknown. All the children were reported normal

II 7 (not examined) reported normal, and one child normal

II 9 Mr G W (Fig 7 A) gave most of the information along with his wife (Fig. 7 B) He had premature graying of the hair and gray-green irides with suggestion of blepharophimosis. His nose root is broad and somewhat thickened but this is difficult to assess in Negroes. His wife showed no signs. We were unable to do audiologic or vestibular tests on either one Their eight children are described in Generation III

Generation III

The following were examined, including auditory and vestibular function

TABLE 1 *Survey of findings in family W I TT*

= With deep brown scl ral ri g; = blu sect r at 7 o clock; = blue sector at 6 'clock; = blue sector at 12 d 3 o clock; = blu sector at 12 o clock

General D = Deceased; M = male F = f male; NK = n t known or not tested; + = trait present; ± = borderline trait 0 = trait or response absent.

Cochlear and vestibular A = Air cond cti n test; B = bone conducti n test; RB = barany otation (basic) RM = barany rot ti n (ma s) CB = cold w t r cal ric test (basic); CM = cold water caloric test (mass) Lred = sligl tly reduced response m.red = m rkedly reduced respo se

Sex	Dys. canthi medialis lat.	Prominent nose	Hyperplasia supercilii	Iris pigmentation Right	Iris pigmentation Left	White forelock	Inter-ocular index	Cochlear response Right	Cochlear response Left	Vestibular response Right	Vestibular response Left
M	NK	NK	NK	NK		Prem. gray	NK	Reported good		NK	
F	NK	NK	NK	NK		0	NK	Reported good		NK	
F	NK	NK	NK	Blue	Blue	+	NK	Congenital deaf		NK	
M	NK	NK	NK	Brown	Brown	±	NK	Congenital deaf		NK	
I	NK	NK	NK	Brown	Brown	0	NK	Reported good		NK	
M	NK	NK	NK	Brown	Brown	0	NK	Reported good		NK	
M	±	+	0	Green + brown	Green + brown	Prem. gray	NK	Normal		NK	
F	0	0	0	Brown	Brown	0	NI	Normal		NK	
F nda	+	0	0	Bl	Brow	Eye browns	0.58	Congenital deaf		RB. 0 RM. 0 CB. 0	0 0 0
F	NK	NK	NK	Blue	Blue	0	NK	Congenital deaf		NK	
NK	NK	NK	NK	Brown	Brown	0		Reported good		NK	
M	NK	NK	NK	Brow	Brown	0		Reported good		NK	
F	0	0	0	Brown	Blue	Few hairs	NK	Congenital deaf		RB 0 RM 0	0 0
F	NK	NK	NK	Brown	Brown	NK	NK	Reported good		NK	
M	+	+	0	Blue	Green + brown	0	NK	Cong. deaf	Norm l	RB 0 RM. NK	Normal NK
M	0	0	0	Deep brow	Deep brown	0	NK	Reported good		NK	
M	+	0	±	Deep brown	Deep brown	0	0.03	A Dip t B: 2000 cps Normal	Normal Normal	RB: red CB. Normal	sl.red. Normal
F	0	0	±	Deep brown	Deep brown	0	0.51	N rmal		RB. red. CB. Normal	sl red. red.
F	+	+	0	Light brown	Light brown	0	0.61	Cong nital deaf		RB. 0 CB 0	0 0
M	0	0	0	Deep brown	Deep brown	0	0.56	A: sl.red. B. Norm l	sl.red. Normal	RB. red. CB: Normal	sl.red. sl.red
F	±	±	0	Blu	Bl	0	0.58	Congenital deaf		RB. Normal RM. Normal CB. sl.red.	Normal Normal sl.red.

TABLE 1 (*Continued*)

	Birth dat	Sex	Dys. canthi medialis lat	Prominent nose	Hyperplasia supercili	Iris pigmentation Right	Iris pigmentation Left	White forelock	Inter-ocular index	Cochlear response Right	Cochlear response Left	Vestibular resp. Right
	1936	F	0	0	0	Deep brown	Deep brown	±	0.51	*Dip at 500+1000* air bone		RB: m.red. RM. m.red. CB. 0 CM. red.
	1937	M	0	0	0	Deep brown	Deep brown	0	0.53	A. red. B: 1000	red.	RB: red. RM. red. CB: red. CM red.
	1959	F	+	+	0	Blue	Brown	0	0.57	Congenital deaf		RB: 0 RM *0*
	1960	M	0	±	0	Deep brown	Deep brown	0	0.55	Mod. red. air bone		RB: sl.red. rot.nyst.
	1963	F	+	+	0	Deep brown	Deep brown	0	NK	Appears to hear well		NK
	NK	M				Reported normal				Reported normal		NK
	1955	M	±	±	0	Deep brown	Deep brown	0	0.54	Normal		Normal
	1956	M	0	0	0	Deep *brown*	Deep *brown*	0	0 4_	Normal		RB sl.red.
0	1957	M	NK	NK	NK	Deep brow	Deep brown	NK	NK	NK		NK
.1	1958	F	0	±	0	Deep brown	Deep bro n	0	0.51	Normal		RB. m.red. vert.nyst. RM: m.red. vert.nyst. CB: 0
12	1960	F	left	±	0	Deep brow	Deep brown	0	0 49	Normal		RB: Normal RM. Normal
13	1961	M	0	0	0	Bl	Blue	0	0.49	Congenital deaf		RB: 0 RM 0

III 2, probanda (Fig 1) showed all the features, with white hairs at medial parts of the eyebrows. She was congenitally deaf and had absent vestibular function

III 21 is congenitally deaf with a few possible gray strands in head hair and heterochromia She had absent vestibular function.

III 23 is congenitally deaf on right (Fig. 8) the side of his blue iris. Absent vestibular function also on the right

III 25 had dystopia, sensorineural dip at 2000 cps. on the right, normal left (Fig 12) with altered vestibular function, particularly on the right.

III 26 had no signs except for questionable broad nose root He had normal hearing but altered vestibular function.

TABLE 1 *Survey of findings in family W I TT*

= With deep brown scleral ring; = blue sector at 7 o clock; = blue sector at 6 o lock; = bl sect r at 12 and 3 o clock = bl e sect r t 12 clock.

Gen ral D = Deceased M = m le; F = femal ; NK = not known or not tested + = trait present ± = borderlin trait; 0 = trait or response absent.

Cochlear and vestibul A = Air conducti n test; B = bone conduction test RB = barany rotati n (basic) RM = barany rotation (mass) CB = cold w ter cal ric test (basic) CM = cold wate caloric test (mass) sl.red. = slightly reduced response m.red = markedly reduced respo se

	Sex	Dys. canthi medialis lat.	Prominent nose	Hyperplasia supercilii	Iris pigmentation Right	Iris pigmentation Left	White forelock	Inter-ocular index	Cochlear response Right	Cochlear response Left	Vestibular response Right	Vestibular response Left
e	M	NK	NK	NK	NK		Prem. gray	NK	Reported good		NK	
k	F	NK	NK	NK	NK		0	NK	Reported good		NK	
	F	NK	NK	NK	Blue	Blue	+	NK	Congenital deaf		NK	
	M	NK	NK	NK	Brown	Brown	±	NK	Congenital deaf		NK	
	F	NK	NK	NK	Brown	Brown	0	NK	Reported good		NK	
	M	NK	NK	NK	Brow	Brown	0	NK	Reported good		NK	
	M	±	+	0	Green + brown	Green + brown	Prem. gray	NK	Normal		NK	
	F	0	0	0	Brown	Brown	0	NK	Normal		NK	
. unda	F	+	0	0	Blue	Brown	Eye- brows	0.58	Congenital deaf		RB. 0 RM. 0 CB 0	0 0 0
	F	NK	NK	NK	Blue	Blue	0	NK	Congenital deaf		NK	
	NK	NK	NK	NK	Brown	Brown	0		Reported good		NK	
	M	NK	NK	NK	Brown	Brown	0		Reported good		NK	
)	F	0	0	0	Brown[4]	Bl	Few hairs	NK	Congenital deaf		RB. 0 RM. 0	0 0
7	F	NK	NK	NK	Bro n	Brown	NK	NK	Reported good		NK	
3	M	+	+	0	Blue*	Green + brown	0	NK	Cong. deaf	Normal	RB. 0 RM. NK	Normal NK
)	M	0	0	0	Deep brown	Deep brown	0	NK	Reported good		NK	
1	M	+	0	±	Deep brown	Deep brow	0	0.63	A. Dip t B. 2000 cps	Normal Normal	RB. red. CB. Normal	sl.red. Normal
4	F	0	0	±	Deep brown	Deep brown	0	0.51	Normal		RB. red. CB. Normal	sl.red. red.
7	F	+	+	0	Light brow	Light brown	0	0.61	Congenital deaf		RB. 0 CB 0	0 0
9	M	0	0	0	Deep brown	Deep brown	0	0.50	A. sl.red. B. Normal	sl.red. Normal	RB red. CB. Normal	sl.red. sl.red.
5	F	±	±	0	Blue	Blu	0	0.58	Congenital deaf		RB. Normal RM. Normal CB. l.red.	Normal Normal sl.red.

TABLE 1 (*Continued*)

Pedigree No.	Birth date	Sex	Dys. canthi medialis lat.	Prominent nose	Hyperplasia supercilii	Iris pigmentation Right	Iris pigmentation Left	White forelock	Inter-ocular index	Cochlear response Right	Cochlear response Left	Vestibular r... Right
IV 2	1936	F	0	0	0	Deep brown	Deep brown	±	0.61	Dip at 500+1000 air bone		RB. m.red. RM m.red. CB: 0 CM: red.
IV 3	1937	M	0	0	0	Deep brown	Deep brown	0	0.55	A. red. B: 1000	red	RB. red. RM red CB. red. CM red.
IV-4	1959	F	+	+	0	Blue	Bro	0	0.57	*Congenital deaf*		RB 0 RM: 0
IV-5	1960	M	0	±	0	Deep brown	Deep brown	0	0.55	Mod. red. air bone		RB sl.red rot.nyst.
IV-6	1965	F	+	+	0	Deep brown	Deep brown	0	NK	Appears to hear well		NK
IV 7	NK	M				Reported normal				Reported normal		NK
IV-8	1955	M	±	±	0	Deep brown	Deep brown	0	0.54	Normal		Norm
IV 9	1956	M	0	0	0	Deep brown	Deep brown	0	0.42	Normal		RB. sl red.
IV 10	1957	M	NK	NK	NK	Deep brown	Deep brown	NK	NK	NK		[illegible]
IV 11	1958	F	0	±	0	Deep brown	Deep brown	0	0.51	Normal		RB m.red vert nyst RM: m red vert nyst CB. [illegible]
IV 12	1960	F	left	±	0	Deep brown	Deep brown	0	0.49	Normal		RB. Nor RM Nor
IV 13	1961	M	0	0	0	Blue*	Blue	0	0.49	Congenital deaf		RB [illegible] RM [illegible]

III 2, probanda (Fig. 1) showed all the features, with white [illegible] medial parts of the eyebrows. She was congenitally deaf and had [illegible] vestibular function.

III 21 is congenitally deaf with a few possible gray strands in head [illegible] and heterochromia. She had absent vestibular function

III 23 is congenitally deaf on right (Fig 8) the side of [illegible] Absent vestibular function also on the right.

III 25 had dystopia, sensorineural dip at 2000 cps. on the right [illegible] normal left (Fig 12) with altered vestibular function, particularly on the right

III 26 had no signs except for questionable broad nose root. [illegible] had normal hearing, but altered vestibular function.

Fig. 7 M t rnal uncl (II-9) f probanda, showi g grav hai which dev loped ea ly (and lso in hi f the I 1) He ha broad nose root and ggestion f blepharophimosis (A) with graygree irides. His wif (II 10) ha n igns (B)

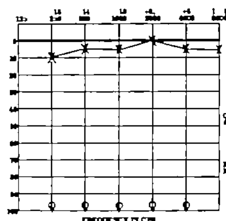
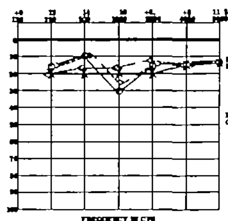


Fig 8



F 9

Fig 8 Audiogram f G W J (III 23) proband first cousin. H has complet sensori neural loss on the right, n rmal h ing the left His heterochromia shows the blu iris on the right.

Fig 9 Audiogram f first son nd third born hild (IV 3) f probanda There is moderat bil teral sensorineural l ss in ll frequencies, with dip t 1000 cps. H had bilat rally reduced estib la f ncti n, particul ly n ight.

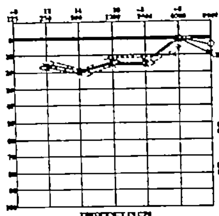


Fig. 10 A diogram f second son, fifth born child (IV 5) f probands. There is a moderate bil teral sensorineural loss i ll frequencies except 4000 and 8000 cps. There wa question f bnormality f estibular response

III 27 had dystopia, heterochromia, was congenitally deaf and had no vestibular response Tomography of her cochlear and vestibular apparatus showed gross deformities (Figs. 13 A and 14 A)

III 28 showed slight air bone conductive loss, due to serous otitis media bilaterally but had altered vestibular function. Tomography of the cochlear and vestibular apparatus is considered normal and is used for comparison with sister (Figs. 13 B and 14 B)



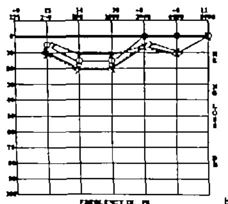


Fig. 11 Second daughter nd second born child (IV 2) of proba ds. There were no out ward signs (A) of the y drome, but udiogram (B) how mod rat bil teral sensorineural loss i middl frequencies. Her estibul f ncti wa grossly bnormal rotation nd caloric tests.

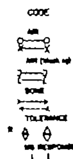


Fig 16. Code to all audiograms.

IV 9 no findings except for altered vestibular function

IV 11 questionable broad nose root No outward signs. Normal hearing Grossly altered vestibular function bilaterally

IV 12 had left dystopia, questionable broad nose root Normal hearing Questionable altered vestibular function.

IV 13 had bilateral isochromic deep blue eyes, no other signs Congenital deafness. Absent vestibular function

Not examined or tested are

IV 7 was reported normal

IV 10 reported normal in all respects.

DISCUSSION

In the examination of the 53 members of four generations, it was possible to assemble a complete pedigree, 22 of whom received detailed investigation including careful auditory and vestibular evaluation. Following Waardenburg's description and keeping in mind that not all the features may be found in any one individual (Fisch 1959 DiGeorge, 1960 Campbell, 1962 Partington, 1964) it would appear that 20 members of our pedigree were affected (4 of whom were not examined) They showed one or more of the signs of the syndrome although some had only one and often this was a borderline or questionable trait

Dystopia Inasmuch as they were Negroes, the greatest difficulty in our group was in assessing the presence, or extent of dystopia, which is reported to be the symptom of greatest penetrance For measurement we used the methods advocated by many of the authors and adopted the ratio recommended by Partington (1964) Some of what we called dystopia with broad nose root when the index was calculated, fell into Partington's normal range, or at the lower end of the abnormal range There were only four members examined whose interocular index was 0.58 or above, and

the highest was 0.64. In two, the index was less than 0.58, but yet their appearance was so much different from other members of the family that the dystopia was considered to be present.

Broad nose root (hyperplasia radicis nasi). The prominent nose root again was difficult to assess, but those in whom it appeared looked considerably different from the others, and it was concluded that five showed this symptom, and five were borderline or questionable. Once again the question of the Negro physiognomy would be of considerable importance here and certainly there must be many intra racial variations.

Hyperplasia of medial portion of eyebrows. None definite found.

Iris pigmentation. Seven of the affected members had heterochromia or isochromic blue eyes, one of whom (II 2 probanda's mother) was not examined, but described by all who knew her as having deep blue eyes. In those of our patients with this feature we were very much impressed with the striking blueness of the eyes with the deep brown circumcorneal pigment layer which shows up well especially in Fig. 3 A. There were no other prominent eye findings, nor abnormal pigmentation of the fundus, but in a few instances the ophthalmologist reported Type III optic discs, a deep physiologic cupping. This may be a coincidental finding.

White forelock. White forelock occurred in only one definitely (II 2, probanda's mother) but she was not examined.

Probanda had a few white hairs at the medial portion of her eyebrows, her uncle (II 9) and her maternal grandfather (I 1) were prematurely gray, and there were questionable white head hairs near the midline in III 21 and IV 2.

Congenital deafness. There were 9 members who were congenitally deaf with mutism, three of whom were not examined, but are so closely related and so completely reported by informants that there would be no doubt of this condition being genuine. Furthermore one was congenitally deaf on one ear (Fig. 8) and there were four others (Figs. 9–12) with moderate bilateral sensorineural losses, of somewhat unusual configuration.

The unilateral losses have previously been described by Waardenburg (1951), Fisch (1959), DiGeorge (1960), Partington (1964) and Francois (1965). DiGeorge (1960) has alluded to "mild or moderate bilateral impairment of hearing" but there was no demonstration by audiogram of this statement. The only reference to this in his text is described on audiometric testing as having a "mild conduction loss in the high frequencies, but bone conduction was normal". As a matter of fact, Fisch (1959) is quite explicit in stating that *"bilateral hearing loss with the moderate type in both ears was never observed"* (his italics). Our descriptions of mild bilateral sensorineural losses therefore would appear to be an additional finding in this syndrome. Some of our mild loss curves bear a striking resemblance except in lesser degree to Fisch's unilateral moderate representation, particularly those showing a gradually improving threshold for higher frequencies.

Francois confirmed Fisch s findings and reiterated his statement that the moderate ascending curve audiogram is most often unilateral and "is never bilateral in the Waardenburg syndrome Should a bilateral middle frequency auditory dip be present however another cause should be con sidered

Francois noted the occurrence of the profound unilateral loss on the side of the depigmented eye and we found this in one instance (III 23) al though the opposite eye was not the usual deep brown (Fig 8)

The most striking findings, however were in our vestibular function evaluations There was no response to any vestibular function test in 5 of the 6 bilaterally congenitally deaf members of the family that we examined. On the other hand one of the bilaterally congenitally deaf children (IV 1) surprisingly gave a normal response to both rotation tests, and only slightly reduced bilaterally to cold caloric (basic) stimulation

Our one patient with congenital unilateral loss gave no response on the affected side to rotation testing

Four of the children with mild to moderate sensorineural losses showed some vestibular function alteration on either rotation or caloric testing or both, sometimes on both ears, occasionally one ear for rotation, or the other ear on caloric testing

In three children with normal hearing there was again the variable response on one or both ears to either rotation or caloric testing This was particularly marked in IV 11 with no syndrome signs, with normal hearing, but with grossly abnormal response to both rotational and caloric tests. This was seen to a lesser extent in the patient (III 28) who had a mild bilateral conductive loss secondary to serous otitis media

Of all 18 patients in the family in only one instance was there com pletely normal vestibular function (IV-8) It is difficult to explain on the face of it, the abnormal vestibular function occurring so widely throughout the family regardless of the other signs and in spite of normal hearing in some instances

It was felt perhaps that it might be a special response for this particular family or that somehow some type of medication could have been used in all However all history and other physical findings gave no indication of any adventitious vestibular effect

It was also considered that perhaps such testing in children might be somewhat uneven in terms of end point, cooperation and reliability Never theless, it was found during the course of this study that one part of the family had been tested independently at another institution. The results from each tester unknown to the other and done at considerably different intervals, were quite similar and in most instances almost exactly the same

At this point it was decided to do the recently developed tomographic x ray studies of the temporal bones (Valvassori, 1963 A, B 1964) It was found that there were definite structural changes noted in both the coch

lear and vestibular labyrinths in III 27 a nine-year-old girl who had the most marked dystopia of our group, prominent nose root, light brown eyes, complete congenital deafness and no response to rotation or caloric tests (Figs. 13 A and 14 A) Her brother III 28, had no outward signs, a slight conductive loss secondary to serous otitis media, and his cochlear and vestibular labyrinths are considered normal on tomographic projection (Figs. 13 B and 14 B) Nevertheless, he too had a change on vestibular function tests.

Searching the literature for clues to explain these wide ranging vestibular responses, we find that Mende reported on vestibular function in three of her cases, showing that there was no cochlear response in any that one had normal vestibular response (presumably to rotation) and the other two showed no responses (again presumably to rotation) until the right ear in each child, was irrigated with ice water Arnvig (1959) said that in Waardenburg's syndrome the vestibular organ is often involved "as is frequently the case with inherited hearing impairment" but unfortunately did not give his results In Zelig's case report on an Israeli Indian boy there was no audiometric response or vestibular response to rotation or caloric tests.

Stoller's patient shows Fisch's Type I audiogram bilaterally and no response to rotation or caloric tests (child had pneumonia and might possibly have had ototoxic medication)

Although Waardenburg did no specific audiometric or vestibular function studies, he was quite aware of the various genetic aspects of deaf mutism and cites particularly one type of dominant labyrinthine deafness, but without other features of the syndrome. This was described by Müller (in Waardenburg) as being a deafmutism with vestibular disturbance in different generations. The histologic picture demonstrates a hypoplasia of the bony cochlea and particularly of the modiolus, with defective cochlear nerve and alterations of the sense elements and of the sacculus. However the semicircular canals and utriculus are normal

The histologic findings would seem to fall into the category of the aplasias, of genetic origin, particularly of the Mondini type. Schuknecht's recent classification of deafness of genetic origin includes histologic descriptions of many of these but none with Waardenburg's syndrome Fisch (1959) has shown the histologic picture in one of his patients with Waardenburg's syndrome which in our view resembles the Scheibe type of aplasia, mostly confined to the membranous labyrinth, but sparing the semi-circular canals and both the utricle and saccule. Serial sections of the auditory nuclei and higher brain areas were also done by Fisch's group and reported as normal.

It is possible that some of the paradoxical vestibular responses in our patients may represent some type of central nervous system disorder but it probably is an end organ disturbance which will require further definition

SUMMARY

Our own findings with the demonstrated bony abnormality in x ray tomography suggest the possibility of various kinds of aplasias occurring in Waardenburg's syndrome, including the Mondini, Scheibe, and Alexander types, involving the osseous and membranous labyrinths.

Furthermore, it appears that the labyrinthine involvement is widespread throughout most of the members of this family regardless of the other features of the syndrome and, in testing, may be grossly observable or quite subtle in its manifestations. In our family at least, the vestibular malfunction was the most prominent feature, more so than the sensorineural hearing loss, and appeared in a number of the children who had normal hearing and no outward signs of the syndrome

It is hoped that our findings will be corroborated by others, or that histologic evidence of end organ lesion or other sensorineural changes will become available In the meantime otologists very likely will find it necessary to consider Waardenburg's syndrome, as well as other genetic defects, in their differential diagnoses of bilateral congenital hearing loss in very young children

Also the same possibilities exist in unilateral hearing losses, severe or moderate. From our own findings, even mild bilateral sensorineural losses may occur as part of the syndrome

Vestibular function tests would be recommended in all instances, since this may be the major indicator of the inner ear defect, and it appears that proper use of x-ray tomography will be of increasing value in determining the presence of osseous labyrinthine changes. Membranous changes in the cochlear and vestibular labyrinth will have to await further definitive studies and histologic evaluation

Ophthalmologic evaluation may be helpful in defining the eye signs in the syndrome even in the absence of deafness, and the ophthalmologist may be the first to uncover the presence of the syndrome, particularly if he knows that no deafness, or mild or moderate losses may occur In any case, ophthalmologic consultation is indicated in suspected cases of Waardenburg's syndrome with deafness, particularly for the determination of iris stromal hypoplasia.

Other studies are contemplated, and will include full audiologic evaluations, including recruitment, small increment sensitivity tests, frequency discrimination, Békésy and other 8th nerve audiometry and discrimination for speech These studies should help to define the sensorineural component in the auditory system

Further vestibular studies are also contemplated to include nystagmography and other aspects of static labyrinth function. It is felt that these studies should explain much about the altered vestibular function in general, particularly in children.

Finally studies are planned to set standards for size and configuration in x-ray tomograms of normal cochleae vestibules, and semi-circular canals. It is hoped that the enigma of diagnosis of congenital hearing loss in children may be made somewhat less portentous than it now is, and perhaps lead the way to an understanding of prevention and even treatment of these complex sensory lesions.

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APPENDIX A

TABLE 2 *Annotated chronology of presentation or publication*

	Author	Year	Country of origin or race	Cases	Pedigree or family
(1)	Van der Hoeve	1916	Dutch	3	None
(2)	Zak	1922	Hungary	?	? One
(3)	Mende	1926	Germany	4	One (complete)
(4)	Waardenburg	1947			
(5)	Goedbloed	1947			
(6)	Walsh	1947	USA	3	None
(7)	Klein	1947			
(8)	Waardenburg	1948	Dutch	1	None
	Klein	1950	Switzerland	1	None
(9)	Waardenburg	1951	Dutch	14	11 (comp.), 1 (part.)
	Keizer	1952	Dutch	2	Family only
	Fisch & Renwick	1954	England	?	10 families
	Buchler	1955	Switzerland	2	2 pedigrees (complete)
	Klenka	1956	Czechoslovakia	Survey	None
	Wildervanck	1957	Dutch	5	Family (partial)
	DeGeorge	1957	USA (white and negro)	7	2 families
+	McKenzie	1958	England	1 (one)	Pedigree (partial)
	Galvez Montes	1958	Spain	No deaf	Family
	Delmarcelle-Pivont	1958	Belgium	?	?
	Meunier Kuhn	1958	France	?	?
	Partington	1959	England	1	Pedigree
+ +	Arnvig	1959	Denmark	4	4 pedigrees
+	Fisch	1959	England	35	3 pedigrees
	LaVergne	1959	Belgium	1	Pedigree
(10)	Nicolaisen	1959	Norway	2	?
	DeGeorge	1960	USA (white and negro)	11	3 pedigrees
	Zelig	1961	Israel-India	1	Family
	Settelmayer & Hogan	1961	USA (mixed ancestry)	1 (no deaf)	Family
	Ray	1961	England	2*	Pedigree
	Scott, Beukering	1962	Africa (Bantu)	1	None
	Stoller	1962	USA	1**	None
	Owsley	1962	USA (Schools for the deaf)	62	None
	De la Harpe	1962	South Africa (coloured)	1	Pedigree
	Campbell et al.	1962	USA	2	Family
	Calnikos	1963	South Africa (Zulu)	1	None
+ +	Thorkilgaard	1963	Denmark	2*	Pedigree
(11)	Aasved	1963	Norway	1	Pedigree
	Jain & Chander	1963	India	1 (no deaf)	Pedigree (partial)
	Houghton	1964	New Zealand (white and Maori)	2	Family
	Partington	1964	Canada	2*	2 pedigrees
	Robinson & Miller	1965	Canada	1	Pedigree
	Francois et al.	1965	Belgium	102	1 pedigree
	Seuad	1965	South African Tribes	16	2 pedigrees
	Ogura	1966	Japan (to be published)		

(1) (6) Van der Hoeve and Walsh are quoted by Waardenburg after he measured the pictures.

(2) Zsako quoted in M nde

(3) Mend quoted by Waardenburg (1951) and DiGeorge (1960)

(4) Presentation before the Dutch Ophthalmological Society December 1947

(5) Goedbloed t ld Waardenburg of hi case t the Soci ty meeting. N record of publicati n.

(7) Presentati n before Swiss Society of Genetics, August 1947

(8) Publication of case of deaf tailor

(9) Publicati n of all cases a d pedigrees and nnouncement of new syndrome

(10) Nicolaissen quoted in Aasved.

+ DiGeorge states that Fisch pedigree 2 is the same as McKenzie s. McKenzi un aware of Waardenburg's publication.

+ + Thorkilgaard's family identical to first of Arnvig' family

+ + + St ller's patient born i Berlin speculation s t relati n to Mende s family

Other cases found in st dy f family

In ssociation with other yndrome or syndromes

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Acta

OTO LARYNGOLOGICA

SUPPLEMENTUM 220

ON PREDICTIVE EQUATIONS FOR SUBJECTIVE JUDGMENTS OF VERTICAL AND HORIZON IN A FORCE FIELD

M. J CORREIA, W C. HIXSON, and J I NIVEN

ACTA OTO-LARYNGOLOGICA NARVAVÄGEN 16, STOCKHOLM NÖ

ACTA OTO LARYNGOLOGICA

SUPPLEMENTUM 30

From the Naval Aerospace Medical Institute Pensacola, Florida

ON PREDICTIVE EQUATIONS FOR SUBJECTIVE JUDGMENTS OF VERTICAL AND HORIZON IN A FORCE FIELD[1]

M. J CORREIA,[2] W C. HIXSON and J I NIVEN

UPPSALA 1968

The static orientation of an individual to linear force fields has been extensively studied through the use of subjective judgments of the orientation of a force field either during simple tilting in the normal gravitational field or during exposure to the resultant of centripetal and gravitational action in centrifuges. While it has been recognized that such judgments may be influenced by the magnitude as well as by the direction parameters of the field only a few studies have been concerned primarily with establishing separate experimental control of these parameters e g. Schöne (1964) who studied magnitude and direction effects of frontal and sagittal plane stimuli on subjective vertical and subjective horizon judgments, respectively Colenbrander (1963–64) who studied the effects of frontal plane stimuli on the subjective perception of vertical and Miller and Graybiel (1964) who studied the effects of frontal plane stimulation on the subjective perception of horizontal

Only Schöne (1964) however and he for his horizon data only attempted to formulate a predictive equation relating the subjective response to the stimulus. He concluded that subjective perception of horizon could be predicted as a direct linear function of a single force component acting along a plane hypothesized to be that of the sensory epithelium of the utricles. The present paper undertakes to evaluate this and an alternative predictive equation over an extended stimulus range for both the frontal and sagittal planes.

METHOD

Subjects

Four men served as subjects. Two of the subjects (two of the authors) were aware of the possible outcomes of the experiment. The other two subjects were naive with respect to the experimental objectives although both had been practiced in making judgments an operating the visual target equipment.

Apparatus

The primary apparatus of this experiment was the Pensacola Centrifuge Slow Rotation Room I Facility and its bioinstrumentation (Hixson 1963) The experimental conditions of the experiment were achieved by seating subjects in a variable attitude chair fixed to the floor of a free-swinging cradle assembly which was bearing supported at the end of a 20 foot radiu cen trifuge arm During rotation, the entire cradle assembly was allowed to swing radially outboard to the angle defined by the resultant of the applied centripetal and gravitational action. Consequently linear acceleration of vari ble magnitude and fixed direction relative to the subject could be presented by rotation of the centrifuge at selected constant angular velocities. The direction

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of the resultant linear acceleration stimulus was manipulated by varying the attitude of the chair permitting the subject to be tilted at various angles relative to the resultant which always remained directed along an axis essentially at right angles to the floor of the cradle.

During the expermental trials the subject s head was fixed to the chair by a helmet which contained custom fitted liners and a compression type chin strap The body was held fixed by a shoulder waist harness assembly

In this experiment two types of targets the technical details of which are described elsewhere (Correia, Hixson & Niven 1965) were used One target consisted of a horizontal luminous rod 7 in long and 1/16 in wide which could be vertically displaced 15 in above or below mean eye level. This linear displacement target was used for subjective estimates of resultant horizon The second target was a similar luminous rod which could be angularly displaced 360 in a clockwise or counterclockwise direction. This angular displacement target was used for subjective estimates of resultant vertical Both targets could be controlled by either the subject or the experimenter at the discretion of the latter

Notation

The linear acceleration stimulus of this experiment, the resultant of an acceleration component directed radially inboard due to centripetal action and a component directed vertically upward due to gravitational action, is symbolized by the vector $\bar{A}$ which can be written as $\bar{A} = |\bar{A}| \angle\phi$ where $|\bar{A}|$ is the absolute magnitude and the angle ϕ the morphological direction of the vector This kinematically based description of the stimulus (Hixson, Niven & Correia, 1966) is referenced to cardinal head axes and planes of the subject by means of the following symbols The axes of an erect right handed rectangular cartesian coordinate reference frame fixed to the head are identified as x y and and denote the front back left right, and vertex base directions where the $+x$ axis is directed toward the front $+y$ toward the left, and $-$ toward the vertex of the skull The frontal midsagittal and horizontal head planes are identified as the y- x and xy planes respectively

These axis and plane symbols are used as subscripts in the $|\bar{A}| \angle\phi$ vector short hand notation to describe the plane in which $\bar{A}$ acts as well as its orientation within this plane. For example with the radial orientation of the subject, the stimulus is identified as $\bar{A} = \bar{A}_{x} = |\bar{A}| \angle\phi$ since the resultant acts in the midsagittal x- plane and changes in its direction within this plane are produced by statically tilting the subject about his y axis The head erect posture serves as reference for measurement of ϕ i e $\phi = 0$ when $\bar{A}$ is aligned with the + head axis ϕ_y is measured as a positive angle when the inboard facing subject is pitched backward from this alignment and as a negative angle when pitched forward (cf Fig 1) Correspondingly for the tangential orientation in which the subject faces away from the direction of rotation, $\bar{A} = \bar{A} = |\bar{A}| \angle\phi$ since the resultant acts in the frontal y head plane and changes in its direction are effected by tilts of the subject about the x axis. For the

erect posture, $\phi = 0$ outboard tilts in the direction of the left shoulder are measured as positive angles and tilts in the opposite direction as negative angles (cf Fig. 2)

The subjective response measured as the angular displacement of the visual target from a given morphological reference is identified by the symbol τ with an appropriate x or y subscript to denote the form of target motion With the linear displacement target, the elevation or depression of the target rod about mean eye level is denoted as τ since the target motions can be equated to rotation about the y head axis Each τ datum is measured as the angular deviation of a line joining the target and the eyes from a plane parallel to the horizontal xy head plane at eye level $\tau = 0$ when the target lies in this reference plane. Target displacements below and above this plane are measured as positive and negative angles respectively The symbol τ is used to identify the response data collected with the angular displacement target since its motions are equivalent to target rotation about the x head axis With this target, τ is measured as 0 when the long dimension of the target rod is aligned with the head axis and as a positi e or negative angle when rotated clockwise or counterclockwise as viewed by the subject away from this alignment.

Procedure

In the first half of the experiment each subject was oriented radially facing the center of rotation and the variable attitude chair adjusted to one of five tilt angles n a counterbalanced order 0 15 inboard 30 inboard 15 outboard and 30 outboard (or $\phi = 0$ -15 -30 $+15$ and $+30$ respectively) For a given chair tilt angle, each subject made five subjective judgments of resultant horizon using the linear displacement target under five levels of acceleration magnitude: $|\bar{A}| = 1.00$ 1 25 1 50 1 75 and 2.00 g All subjects were first exposed to the static 1 00 g stimulus to establish a baseline two subjects then experienced the remaining acceleration levels in ascending order the other two in descending order To minimize transient effects all g transitions were made slowly (90–180 sec.) and an additional 60 sec at constant velocity were allowed to elapse before judgments began. With these stimulus conditions an objective estimate of resultant horizon was achieved when the target was adju ted so that a line joining it to the eyes lay in a plane perpendicular to the resultant $\bar{A}$. Since this target was fixed to the chair in which the subject was tilted a perfect estimate of horizon would be measured always as $\tau = \phi$ degrees

In the second half of the experiment, each subject was oriented tangentially facing away from the direction of rotation tilted ϕ degrees right and left relative to the resultant acceleration and given the task of estimating his perception of resultant ertical i e the direction of $\bar{A}$ Under these conditions a target setting ($= \phi$ corresponds to a perfect estimate of the resultant vertical With these eptions the procedure was identical to that described for the first half f th periment.

RESULTS

The group means for the τ subjective estimate of resultant horizon data are plotted in Fig 1 as a function of the absolute magnitude $|\bar{A}|$ and direction ϕ_r of the resultant acceleration stimulus acting in the sagittal (x-) head plane These data indicate that when the subject was sitting in a head erect posture relative to the stimulus, $\phi = 0$ an increase in acceleration magnitude resulted in τ_r becoming more positive That is each increase in acceleration level was accompanied by a further depression of the target below the horizon observed at the 1 00 g level When the subject was statically pitched back 15 and 30 toward the supine position ($\phi = +15$ and $\phi = +30°$) relative to the stimulus similar depressions of the horizon data were noted The same observation held when the subject was statically pitched 15

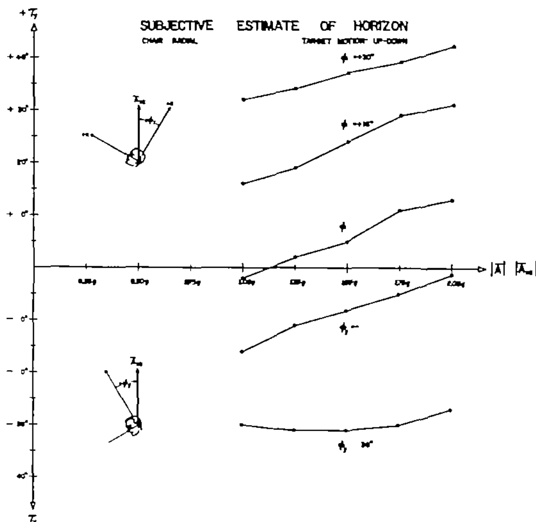
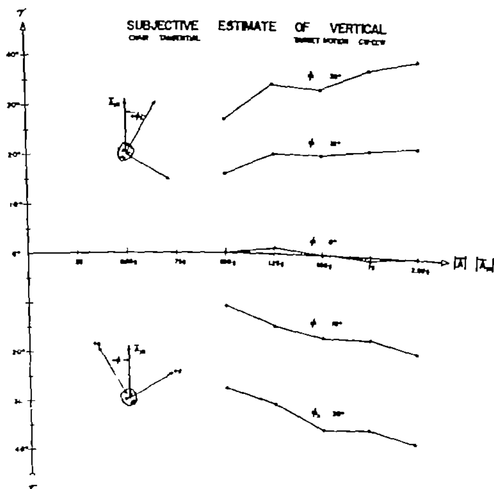


Fig. 1 Mean estimates of resultant horizon τ as a function of the magnitude of the resultant linear acceleration for various body tilts.

toward the prone posture ($\phi = -15°$) However when the subject was pitched forward 15 further ($\phi = -30$) his subjective estimate of resultant horizon was much less affected by the increase in acceleration level.

The group means for the τ subjective estimate of resultant vertical are plotted in Fig 2 as a function of magnitude $|A|$ and direction ϕ of the resultant acceleration stimulus acting in the frontal (y-) head plane These data indicate that when the subject was seated in a head erect posture relative to the force field ($\phi = 0°$) his judgments of vertical were relatively unaffected by changes in acceleration magnitude When the subject was tilted to his left ($\phi = +15$ and $\phi = +30°$) and exposed to accelerations of increasing level increased values of τ in the positive or clockwise direction were observed Similarly when the subject was tilted toward his right ($\phi = -15$ and $\phi = -30°$) and acceleration level increased increased values of τ in



F g. 2. Mean estimates of resultant vertical as function of the magnitude of the resultant linear acceleration f various body tilt

the negative or counterclockwise direction were observed In general except for the head erect posture an increase in acceleration magnitude resulted in the subject s moving the target further away from his vertex base head axis whether he was tilted left or right.

DISCUSSION

The increase in errors in subjective estimation of resultant vertical or resultant horizon due to increase in magnitude of the linear acceleration stimulus for a given direction in the frontal or sagittal plane confirms earlier observations (Miller & Graybiel 1964 Schöne 1964) The finding that there are certain angles where increase in magnitude does not increase errors in estimation of resultant horizon ($\phi = -30°$) and resultant vertical ($\phi = 0°$) also confirms previous work (Miller & Graybiel 1964 Schöne, 1964) However postulations (Schöne 1964) that these estimations are either exclusive functions or linear functions of the $A \sin \phi$ component of the resultant acceleration are not supported over the full stimulus range of the present experiment

When the sagittal plane of the head was tilted relative to the resultant it was observed that for the $\phi = -30$ inclination, changes in the τ judgment did not occur when the magnitude of the stimulus was changed. In effect, τ was independent of stimulus magnitude when the resultant was directed along a null axis tilted back 30 from the head axis in the mid sagittal plane. This axis is shown as $_0$ in Fig. 3 From similar horizon data Schöne (1964) postulated that $_0$ was perpendicular to the equivalent plane of the sensory epithelium of the utricles so that acceleration in this direction

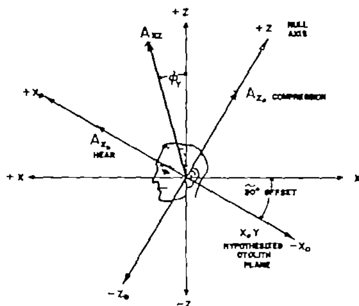


FIG 3. Sketch showing null axis of response and Schone' hypothesized otolith plane to which the A 'shear" and A compression components of the resultant acceleration are referenced.

would exert only pressure (compression) on the otolith membranes according to the pure shear concept of otolith stimulation, such forces should not produce a response He further postulated, in the form of a linear sine expression, that τ was affected only by the component of the resultant which acted along axis x which, in conjunction with the y head axis, defined the plane of his hypothesized receptor and that τ_r was a linear function of this component over the stimulus range of his experiments

With the notation of this paper as depicted in Fig. 3 A represents the component acting along axis x_s in Schöne s hypothesized $x_s\,y$ otolith plane while A_n represents the component acting at right angles to the plane In the mathematical context, Schöne s postulations require that τ be a linear function of $A_{x_s} = |\bar{A}|\sin(\phi + 30°)$ and be independent of changes in magnitude of $A_n = |\bar{A}|\cos(\phi + 30°)$ In the anatomical context A_x and A_n correspond to his hypothesized "shear" and "compression" directed stimuli Of primary concern to this paper is the evaluation of Schöne s hypothesis that accelerations in the plane at right angles to the null axis serve as the critical stimulus parameters accounting for the observed responses

A plot of Schöne s (1964) horizon data for representative values of ϕ and $|\bar{A}|$ is shown in Fig. 4 as a function of the hypothesized critical stimulus

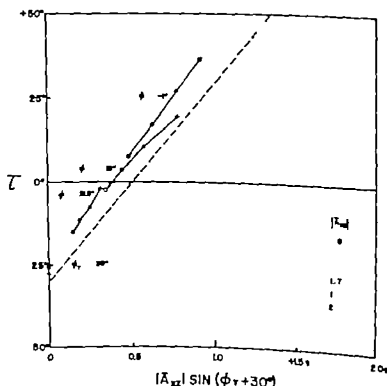
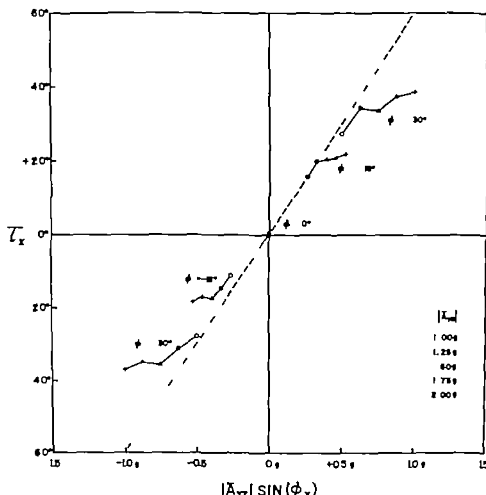


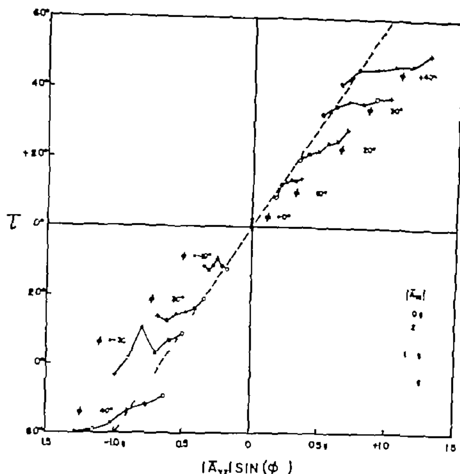
Fig. 4 Subjective height of horizon data (adapted from Schöne, 1964). The response measure, expressed as τ_r, is plotted as function of the A ("shear") component of the resultant acceleration.



F g. 7 Subjective resultant vertical data present study The response measure expressed as $_x$, plotted as a function of the A_y (shear") component of th resultant cceleration.

A similar analysis was performed on the centrifuge data obtained on eight subjects by Miller and Graybiel (1964) in their investigation of the effect of magnitude and direction variations of frontal plane stimuli on the visual per ception of subjective horizontal This response measure is the equivalent of the τ measure of this study in the sense that the objective target alignments are complementary Their data when plotted as a function of A in Fig. 8 offer further evidence that the perception of resultant vertical is not a linear function of this component of the resultant. The dashed diagonal line drawn through $\tau = \pm 30$ $A = \pm 0.5\ g$ coordinates for slope reference purposes allows one to observe the increasing nonlinearity between A (shear) and the related response measure at the higher acceleration levels.

Next an analysis was made of Colenbrander s (1963–64) subjective visual *perception of vertical data obtained from a single subject on a centrifuge* by tilt of the head relative to the torso A plot of his data as a function of A is presented in Fig 9 Again the subjective estimate of vertical is not a lin ear function of A_y, this component clearly loses its effectiveness to influence

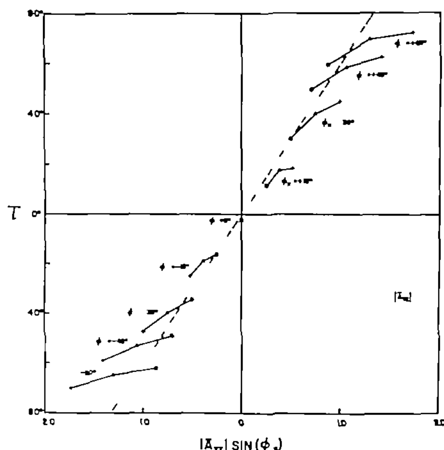


F G. 9 Egocentric visual localization f the horizontal data (dapted from Miller a d Graybiel, 1964). The response measure expressed a ,, is plotted as function of A_y ("shear") component of the acceleration stim lus.

τ at the higher acceleration levels. Further for these data there is no ques tion of the potential for discontinuities in τ for identical values of A_y.

Although Schöne (1964) did not plot his subjective perception of vertical data as a function of A_y, convincing support for nonlinearity and the existence of discontinuities is available from these data also The data, collected from a single subject involve two different acceleration levels, |$\bar{A}$ | = 1 0 and 2 0 g and a selected series of leftward-directed body tilt angles over the φ = 0 to 180 ranges. A plot of these data over the 0 < φ < 90 quadrant as a function of A is presented in Fig 10 Comparison of the slope of the data with the slope reference line again establishes the nonlinearity of the response

The problem then becomes one of finding a function expressible in terms of the stimulus which will allow the development of a predictive equation of the τ and τ estimates of horizon and vertical to be expected when head tilts are made in force fields of different magnitude The limiting condition is



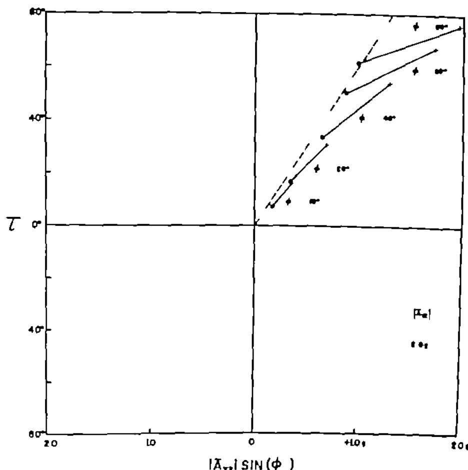
F G. 9 Subjective plumb line data (adapted from Colenbrander 1963–64). The response measure expressed as $_{x}$ is plotted as function of A_y ("shear").

that the function whether it be linearly or nonlinearly related to the response eliminate the discontinuities observed with A sin ϕ i e that identical values of the function predict identical values for τ

Analysis of the data showed that A tan ϕ the product of the relative intensity A of the field and the tangent of the angle ϕ the resultant describes relative to the $_s$ null axis served both to improve the fit and eliminate the discontinuities of the τ data observed at the higher stimulus levels In addition the response is linearly related to this function at relatively low stimulus levels and becomes nonlinear at the higher levels a trend which is in accordance with the data.

The tangent function when made specific for the subjective horizon data becomes $|A$ $|$ tan (ϕ $+30°$) for the sagittal plane. A plot of the related τ subjective horizon data versus this function for all of the stimulus configurations is presented in Fig 11 It is immediately apparent that the discontinuities observed in Fig 5 when the τ data were plotted as a function of A are virtually nonexistent with this tangent function

Moreover by applying a simple arctan conversion to A tan ϕ a predictive equation for the response results which well describes the observed nonline-



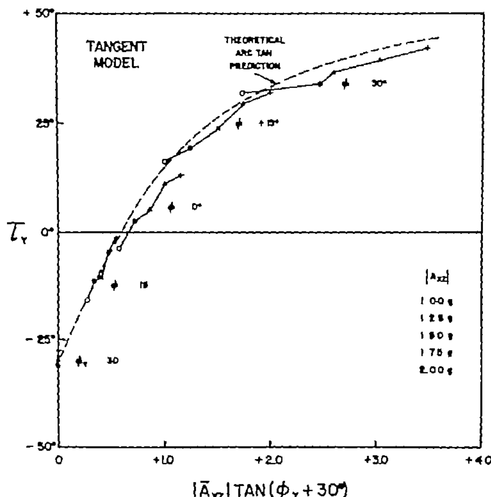
F o. 10. Subjective vertical data (adapted from Schöne, 1961) Th response measure xpressed as τ_p is plotted as function of A_y ("shear").

arity This conversion, plotted as a dashed curve in Fig. 11 and described by the equation

$$\tau = \text{arc tan}\,[\,|\bar{A}\ \ |\tan(\phi\ +30\ )] - 30 \qquad (1)$$

not only predicts the trend but quantifies the absolute numerical value of the data With this conversion the response equation in its basic form is τ = arc tan A tan ϕ where A = magnitude of resultant linear acceleration and ϕ = tilt angle. When this expression is transformed t tan τ = A tan ϕ and plotted for the various stimulus configurations a linear straight line fit of th transformed data would be predicted

Correspondingly the A tan ϕ function becomes specific f r the frontal plane stimulus when expressed as $|\bar{A}\ \ |$ tan ϕ_p. Plots f the r data derly d from the present study and the studies of Miller and Graybiel (1961) (a l n brander (1963–64) and Schöne (1964) are presented in Figs 12 1((Th data



F 11 Subjective resultant horizon data of present study The response measure expressed as plotted against the sagittal plane tangent function. The dashed curve represents the theoretical response prediction of the "arc tan conversion of the tangent function.

of these figures are identical to those shown in Figs 7–10) The arc tan conversion for the frontal plane described by

$$\tau = \text{arc tan } |A_y| \tan \phi \qquad (2)$$

is shown plotted as a dashed curve in each of these figures. As with the τ_y data the arc tan conversion describes the nonlinear trend of the τ data with the best elimination of discontinuities achieved for Colenbrander s data It should be noted that the arc tan conversion was not adjusted individually for each set of data to improve the fit although this could have been done readily

Because of the stress placed on the physical significance of $A \sin \phi$ in the past it is important to realize that $A \tan \phi$ equally can be assigned physical meaning For example consider a mass of weight A resting on a frictionless plane inclined at an angle ϕ relative to the horizontal. A movement of the

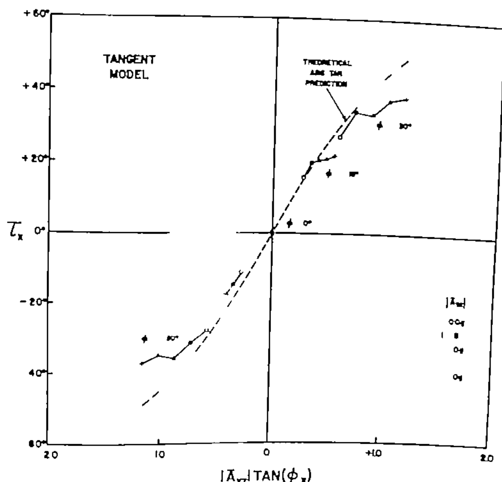


Fig. 12. Subjective resultant vertical data of present study. The response measure expressed as ... is plotted against the frontal plane tangent function.

mass down the plane may be prevented by a force acting parallel to the plane ($A \sin \phi$) equally well it may be prevented by a force acting parallel to the horizontal ($A \tan \phi$)

To summarize the data of this study indicate that the subjective visual perception of resultant vertical and resultant horizon are not linear functions of $A \sin \phi$ as previously postulated from observations over a more limited stimulus range. Further since identical values of this component of the resultant did not lead to identical responses, it is questioned that the response itself can be treated as being even a nonlinear function of only $A \sin \phi$. On the other hand a function $A \tan \phi$ was found which fitted the data without pronounced discontinuities and which, through an arc tan conversion led to the development of a quantitative predictive equation for the visual perception of orientation in gravitational and supragravitational force fields.

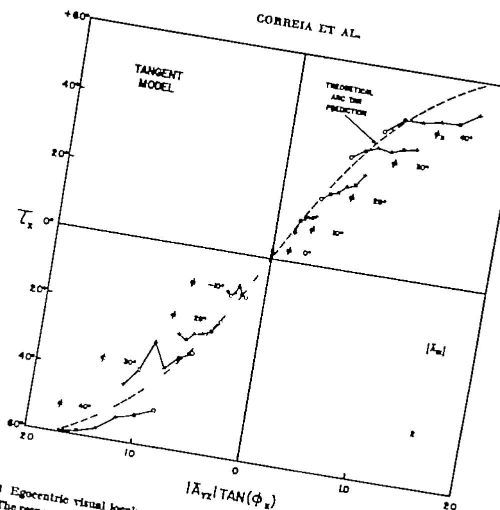


Fig 13 Egocentric visual localization of the horizontal data (adapted from Miller & Graybiel, 1961). The response measure expressed as τ_x, is plotted against the frontal plane tangent function.

Fig 14 Subjective plumb line data (adapted from Colenbrander 1963–64). The response measure expressed as τ_x, is plotted against the frontal plane tangent function.

Fig. 15. Subjective vertical data (adapted from Schöne, 1964). The response measure ... τ_x, is plotted against the frontal plane tangent function.

TANGENT MODEL

THEORETICAL "ARC TAN" PREDICTION

40°

τ 0°

40°

80°

40 20 0 20 0

$|\bar{A}_{YZ}| \, TAN(\phi)$

F a. 14

80°

TANGENT MODEL

THEORETICAL ARC TAN PREDICTION

40°

τ 0°

40°

80°

ABSTRACT

The visual perception of a force field was obtained by requiring subjects to set an appropriate target to resultant vertical and resultant horizon during exposure to five magnitudes A and five directions ϕ of static linear acceleration varied independently in the frontal and sagittal head planes. The resulting subjective estimates were not found to be a linear function of $A \sin \phi$ as has been previously postulated from data collected over a more limited stimulus range. In addition, discontinuities in response for identical values of $A \sin \phi$ were observed. The findings are incorporated in a mathematical expression based on $A \tan \phi$ which provides a quantitative prediction of the subjective response. Data from various sources are evaluated in terms of this expression as well as the sine function.

ZUSAMMENFASSUNG

Die Sehwahrnehmung in einem Kraftfeld wurde geprüft, indem Versuchspersonen aufgefordert wurden, eine geeignete Zielmarke der resultierenden Senkrechten und dem resultierenden Horizont anzugleichen während der Einwirkung von fünf Grössen A und fünf Richtungen ϕ einer statischen linearen Beschleunigung, die unabhängig in der frontalen und sagittalen Kopfebene geändert wurden. Die erhaltenen subjektiven Schätzungen erwiesen sich nicht als lineare Funktionen von $A \sin \phi$, wie früher auf Grund von in einem engeren Reizbereich erhaltenen Daten postuliert worden ist. Ausserdem wurden auch Unstetigkeiten in der Beantwortung identischer Werte $A \sin \phi$ gefunden. Die Befunde werden mit einem auf $A \tan \phi$ basierten mathematischen Ausdruck beschrieben, der eine quantitative Voraussage der Antwort der Versuchsperson liefert. Ergebnisse von verschiedenen Quellen werden mit Hilfe dieses Ausdrucks wie auch der sin Funktion ausgewertet.

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